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of the

AMERICAN COLLEGE OF PHYSICIANS

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Program and all details furnished on request to the Executive Secretary.

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1929

ORIGINAL ARTICLES.

THE PERSISTENCE OF A MITRAL STENOTIC MURMUR IN THE PRESENCE OF AURICULAR FIBRILLATION.*

By Cary Eggleston, M.D.,

NEW YORK CITY.

(From the Department of Medicine, Cornell University Medical College, and The Second (Cornell) Medical Division of Bellevue Hospital.)

Mackenzie[1] seems to have been the first to emphasize the disappearance of the mitral presystolic crescendo murmur with the development of auricular fibrillation, which he, at that time, mistakenly called nodal rhythm. The fact of its disappearance was explained by him as due to the cessation of coördinate auricular systole, a fact which he was also the first to demonstrate in man. Since then, it has come to be accepted as almost axiomatic that auricular fibrillation and a mitral presystolic murmur cannot exist together. It is my purpose in the present communication to show that it is not uncommon to encounter patients with rheumatic mitral disease and fibrillation of the auricles in whom a mitral murmur is clearly heard to continue right up to the first sound of the heart. These cases occur so frequently that it is rare for a month to pass without there being one or more to demonstrate to my students. In a considerable proportion of such cases, this murmur sounds definitely crescendo at its termination in presystole, and is, therefore, identical with that murmur which is regarded as most characteristic of mitral stenosis when the regular sinus rhythm is present. I propose to offer evidence in support of the theory that this apparent paradox is due to an auditory misinterpretation produced by the

* Read before the Association of American Physicians at Washington, D. C., May 1, 1928.

shortening of diastole and the accentuation of the first heart sound. The persistence of such a murmur during fibrillation has lead to considerable confusion and it is my further purpose to attempt to clear this up by an analysis of the phenomena as observed clinically in a large number of cases.

The persistent murmur has been recorded by a number of observers. As is to be expected, Mackenzie himself observed and sought to explain this seemingly inconsistent phenomenon. He wrote: "In the careful examination of a large number of these cases of nodal rhythm we find that the first sound has not the sonorous rumble of the normal first sound, but is represented by a sharp, short snap of very brief duration. Preceding this snap, in a very few cases I have heard a brief crescendo murmur, but a venous tracing showed that there was no auricular systole at the normal time. From this, I suggest that the disputants in the matter have hitherto been confusing two separate conditions. As I have already pointed out, the evidences of auricular systole producing a presystolic murmur are indisputable. While the auricular systole is one cause, it is obvious there must be another cause in these cases of nodal rhythm, and I, therefore, accept the view that a slight regurgitation through the mitral orifice at the beginning of ventricular systole may produce the brief presystolic murmur."

The occurrence of a murmur during the stage of presystole in the presence of auricular fibrillation is a phenomenon which has so arrested my attention during a number of years that every patient presenting it has been subjected to detailed auscultatory investigation. The results of these investigations form the subject of the present discussion.

Two different and distinct murmurs occur with stenosis of the mitral valve. The one is an isolated, short murmur occurring synchronously with contraction of the auricles. It may be soft, blowing and rather indistinct, or, less commonly, it may be rough and rumbling. It usually gives the impression to the ear of being crescendo. This murmur is correctly attributed to the influence of auricular systole. To distinguish it from the murmur next to be described it should properly be called the *auriculosystolic* murmur. The use of this term has the dual advantage of being appropriately descriptive and of avoiding, in part at least, confusion with the more common diastolic murmur which is equally characteristic of mitral stenosis. The auriculosystolic murmur is of rather infrequent occurrence.

The second murmur is not limited to presystole, but begins at or before mid-diastole and continues through to end in the first sound of the heart. It is almost always coarse and rumbling and it frequently seems to increase in intensity in presystole so that, to the ear at least, it appears to be clearly crescendo at its ending. This is the murmur which is most commonly present and, as in the case of the

auriculo-systolic murmur, it too, is very commonly called a presystolic murmur. Since this murmur occupies a considerable portion of diastole and is never confined to presystole, it is much better to speak of it as the *diastolic* murmur of mitral stenosis, thus effectively avoiding confusion with the foregoing. The crescendent ending of this diastolic murmur is usually attributed to the influence of auricular systole, although this has been denied by a number of investigators.[2] I shall return to this matter later. These are the murmurs heard when the heart is beating regularly. The common failure to differentiate between them is, I believe, responsible in large measure for the confusion which exists as to the persistence of a presystolic murmur during auricular fibrillation.

In the course of the years during which my investigations have been carried on, there has been opportunity to study a very large number of patients who have presented the combination of mitral stenosis and auricular fibrillation. Never, in my experience, has the isolated, auriculosystolic murmur been heard in these cases. This confirms Lewis,[3] who says in discussing the influence of fibrillation on the mitral presystolic murmur, that the murmur is not found in presystole while the remaining portions of diastole are free from it. On the other hand, Josué and Barbier[4] report one instance of auricular fibrillation in which an isolated, short, crescendo presystolic murmur was heard definitely in the absence of a diastolic rumble. And in 2 of the 4 cases reported by Hart[5] the murmurs are described as, a short, rough, rumbling murmur preceding the loud first sound; and a first sound, preceded by a thrill and a short, harsh crescendo murmur. It is possible that in exceptional instances such as these we are dealing with a murmur produced by slight regurgitation through an incompletely closed mitral valve, occurring just at the inception of ventricular systole, as believed by Reid. However, as stated, it has never been my fortune to have heard this isolated presystolic murmur, and from both the literature and my own experience I conclude that its occurrence must be quite rare.

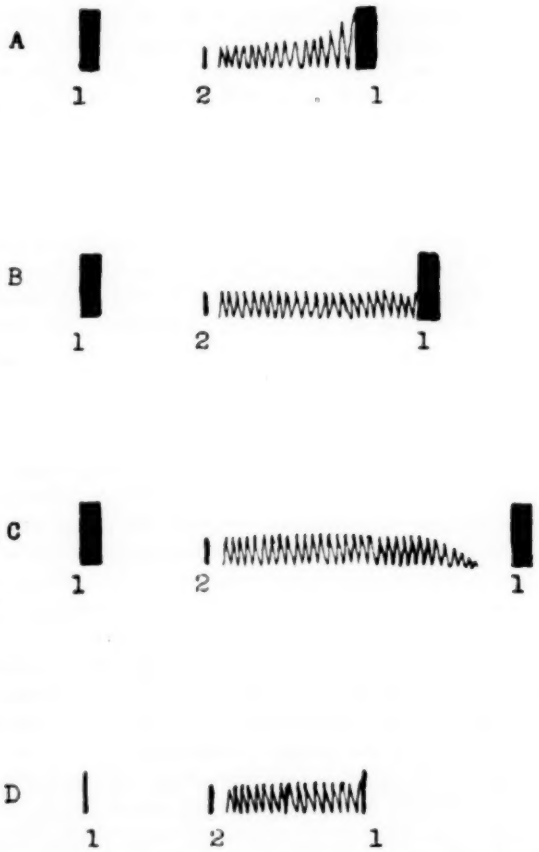
The second type of murmur—the mitral diastolic—which begins at an earlier stage of diastole and then continues through presystole to end in the first heart sound, is the one which may remain after the auricles have passed into fibrillation. Such a murmur is, in a strict sense, presystolic in its termination only. Its persistence has now been observed in more than 40 patients, indicating a much higher incidence than has heretofore been thought to obtain. All of the patients were suffering from rheumatic heart disease and in all the evidences of mitral stenosis were such that this clinical diagnosis could not have been called into question. No patients showing evidences of lesions at other valves have been included. The presence of auricular fibrillation was established by electrocardiograms. Several of the patients who died were proved at autopsy to have had advanced degrees of mitral stenosis with great narrowing of

the orifice. Critical study of this murmur and of its variations as observed in this fairly large group of cases yields the following facts.

The murmur is always of the type usually described as rough, rumbling or purring. It is of low pitch. As already mentioned it invariably starts in diastole at a time definitely earlier than that commonly termed presystole. The murmur rarely seems to be limited to the latter half of diastole. It is always, however, of greater duration than is the brief, isolated auriculosystolic murmur. In the great majority of cases, the murmur fills diastole from the time of its commencement, very shortly after the second sound, right through to the first sound. However long this murmur may be, I have never observed it to become diminuendo in mid-diastole in these patients, as it does fairly often in patients with the regular sinus rhythm. When the first heart sound is short, sharp and much accentuated the impression is given to the ear that the ending of the murmur is reinforced and of crescendo type. This is the case, however, only when the diastolic pause is comparatively brief. The murmur is thus typically developed in all of its characteristics only when the ventricular rate is moderately rapid, usually 100 or more per minute. When the rate lies above 125, diastole becomes so short that the blending of the murmur and the loud, sharp first sound makes the former seem to be quite typically presystolic. Under such circumstances, the murmur may readily be confused with the auriculosystolic murmur as heard in the regularly beating heart. Finally, its auscultatory characteristics in short diastoles as well as in those of moderate length may be compared at will and repeatedly with those in the long diastoles by the simple process of temporarily increasing the heart rate by exercise.

The changes which take place in this murmur when the ventricular rate is markedly slowed following the administration of digitalis, or as the result of rest in bed, suggest the mechanism by which each of its characteristics is produced. Further, since these changes can be studied in one and the same patient we can be sure that we are dealing with the same murmur throughout. The first alteration to be observed is that the duration of the murmur increases as the period of diastole lengthens. Thus it is often found to be of greater length than the total time occupied by diastole at the normal heart rate of 72 per minute. In some patients it is observed to be very much longer than normal diastole. For almost its entire duration it seems to the ear to be of uniformly sustained intensity until shortly before its termination. When diastole is long enough the murmur always stops before the first sound, leaving a period of silence of lesser or greater length. Under these conditions, the ending of the murmur is invariably of more or less rapidly diminishing intensity, so that it dies out rather than stops. This diminuendo termination is as characteristic as is the earlier sustained intensity. These features are illustrated diagrammatically in the accompanying figure.

The fact that the same murmur which fills all of presystole, and perhaps even seems to be crescendo as it ends in the first sound when the heart rate is rapid, can be shown to be long and to cease with a diminuendo ending prior to the first sound when diastole is prolonged, shows that the character of the termination depends largely



Schematic representation of the changes heard in the diastolic murmur of mitral stenosis during fibrillation. 1 indicates the first sound of the heart; 2 indicates the second sound of the heart; *A* shows the seemingly crescendo ending as heard in shorter diastoles; *B* shows the absence of the crescendo ending when diastole is somewhat longer; *C* shows the diminuendo ending and the silence following it in very long diastoles; *D* shows the absence of crescendo ending when the first sound of the heart is feeble.

upon the rate of the heart, or more specifically upon the duration of diastole. In other words, the termination of the murmur is not dependent upon the mechanism of its production, but rather upon the circumstances under which it ends. Thus, when an early appearing systole cuts the murmur off at a time when it is still of full

intensity, its ending is clearly presystolic in time. Further, when the murmur is loud and rough and the first sound is both sharp and greatly accentuated, then its abrupt termination by this sound gives the impression to the ear that the murmur ends with a crescendo reinforcement. When the first sound occurs after the murmur begins to wane, no crescendo appearance is noted, even though the first sound is unchanged. In cases in which the first sound is poorly developed and feeble, a crescendo appearance is not given to the murmur, however early in its course it is terminated by the sound. And, finally, when the murmur is of rushing or blowing type rather than rough and rumbling, its ending does not appear crescendo even when the first sound is loud and sharp. The seemingly crescendo termination is thus seen to be due to the abrupt interruption of an otherwise long, uniformly sustained coarse murmur by a loud and sharp first sound which falls early because diastole is shortened.

Two patients have been studied over a period of several years, both of whom presented clinically typical rheumatic mitral stenosis. Both were observed for some time with regular sinus rhythm and in both the murmur began early in diastole, was well sustained, and, becoming crescendo in presystole, ended in a loud, sharp first sound. In both, the murmur was very rough. Each of these patients developed auricular fibrillation in the course of time, and with its appearance the murmur in each instance remained unchanged so long as the heart rate was more than 100 per minute, except that in occasional long diastoles the termination lost its apparent crescendo character. Slowing of the heart by digitalis brought out the phenomena which have just been described. Acceleration by exercise then caused the murmur to resume its seemingly crescendo ending. In one of the patients the fibrillation lasted less than twenty-four hours, when the normal rhythm was resumed. The murmur remained unaltered. Subsequently, fixed fibrillation developed, and during it the response of the murmur to slowing of the heart was studied with the results mentioned.

A third patient, who first came under observation shortly after the development of fibrillation and in whom all of the features of the murmur were studied during diastoles of widely varying duration, was given quinidin and her heart resumed a sinus rhythm. During the persistence of the normal rhythm—about ten days—no change in the murmur could be detected if the comparison was made with its appearance in the shorter diastoles during fibrillation. In all of the other patients observed, fixed fibrillation was present throughout the whole period of their study.

The most satisfactory conception of the mechanism by which murmurs are produced is that of the formation of a jet, or the *veine fluide* of Chaveau. This mechanism has been reviewed and amplified recently by Reid.[6] Narrowing of the mitral orifice yields almost ideal conditions for the production of a rapidly flowing jet of blood as the stream enters the ventricle. When the stenosis is

marked, the jet should occur throughout the greater part of ventricular diastole. In very pronounced stenosis it should persist until the intraventricular pressure begins to be raised to the level of that in the distended auricles by the onset of ventricular systole. Wiggers[7] says that it is probable that ventricular filling takes place very slowly in the more marked grades of mitral stenosis and continues throughout the entire period of ventricular diastole. He also says that the higher grades of stenosis are always accompanied by diastolic murmurs. Lewis points out that the duration of the murmur depends on the degree of stenosis, the tighter the stenosis the longer the murmur.

The clinical features of the murmur which have been recorded as observed in the presence of fibrillation support this theory of the mechanism of its production. The mechanical and dynamic factors of a tightly constricted mitral orifice, a greatly distended left auricle continually receiving blood under an elevated pressure from the right heart, and a ventricle in which the pressure remains low due to slow and often inadequate filling are such that they must remain essentially unchanged whether the rhythm be regular or the auricles be fibrillating. The only important difference between the two states is the absence during fibrillation of the presystolic auricular contraction. That such a terminal reinforcement of the jet of blood is not necessary for the appearance of what seems to the ear to be a crescendo termination of the murmur is established by its persistence in these cases of fibrillation.

The cause of the crescendo accentuation of the mitral diastolic murmur has been the subject of much argument, and Reid[8] has recently reopened this subject in a series of papers. Reid, like Mackenzie and others whom he cites, contends that the terminal crescendo portion of this murmur is really not a part of the diastolic murmur but is an entirely separate sound produced by brief regurgitation due to the onset of ventricular systole. According to Reid, this mechanism is capable of causing a murmur which would precede the first sound since it would be due to backflow during that brief period which might be expected to elapse before the stretched mitral curtains were snapped taught. While this may be the mechanism involved in rare cases, I believe that the phenomena may be much more simply explained.

The explanation I have to offer is that the murmur under consideration never, in fact, ends with a crescendo reinforcement in the presence of auricular fibrillation. The apparent crescendo ending is an auditory illusion due to the abrupt termination of the rough murmur by the loud, sharply accentuated first sound, which has a pitch that is not widely different from that of the murmur itself. This explanation is in perfect accord with the observed changes which the murmur undergoes with varying lengths of diastole, and with the fact that it has not been observed to appear crescendo when the first sound is weak, however short the diastole.

Further confirmation of the foregoing explanation is found in the simultaneous phonocardiograms and electrocardiograms obtained by Lewis. In 2 patients (tracings 10 to 14 inclusive, p. 257) his records show that the relation of the termination of the murmur to the first heart sound is entirely dependent upon the duration of the diastole in which it occurs. In each patient the murmur was recorded as merging with the first sound when diastole was brief, and as fading out with a definite diminuendo ending in long diastoles, leaving an interval of silence preceding the first sound.

The rôle of auricular systole in the production of the crescendo ending of the mitral diastolic murmur in the presence of the normal sinus rhythm has been called in question on a number of occasions. While it is not my purpose to discuss this subject in the present communication, I should like to suggest that, in such cases too, the crescendo ending may sometimes also be an auditory illusion. Those who deny its being due to auricular systole have so far failed to recognize the possibility that the crescendo appearance may be an artefact produced in the manner here described. At least as much objection may be raised against the theory that it is caused by early regurgitation of blood from the ventricle as to its being merely an auditory deception. Finally, in closing, it should be mentioned that in some cases in which definite crescendo development of the murmur has been heard phonocardiograms have failed to reveal any evidence of an intensification of the sound.[9] Lewis' excellent phonocardiograms also show the absence of a true intensification of the murmur in presystole, as revealed by the amplitude of its vibrations. And Lewis, referring to his sound records, states (p. 249) that a conspicuous crescendo appearance of the murmur is present so infrequently in the phonocardiograms that it seems probable that the crescendo quality as imparted to the ear is rarely formed by the murmur alone, but is really made up of a combination of murmur and first sound.

Summary. 1. A murmur occurs in presystole in a considerable number of patients suffering from mitral stenosis and auricular fibrillation.

2. The presystolic murmur thus heard is a continuation of a murmur beginning earlier in diastole. It is suggested that this murmur should be spoken of as the diastolic murmur of mitral stenosis to differentiate it from the true auriculosystolic murmur.

3. The termination of this murmur in some instances seems to be distinctly crescendo.

4. The crescendo ending is explained as an auditory illusion produced by the merging of the rough murmur with the very loud, sharp first sound. It is not heard when the first sound is feeble, or when the murmur is soft and blowing.

5. The murmur is much prolonged and has a diminuendo ending when heard during long diastoles.

6. It is a valuable diagnostic and prognostic sign since it is

probably found only in the presence of a markedly stenosed mitral orifice.

7. A murmur limited entirely to presystole, with the remainder of diastole free from sound, has not been heard in the presence of auricular fibrillation in a large group of patients. This murmur heard only in the regularly beating heart, should be termed the auriculosystolic murmur.

NOTE.—While this paper was in press an article appeared by Wilhelm Dressler, (Wiener klinische Wochenschrift, 1928, **41**, 1245) in which the author contends that the presystolic murmur is produced in regular hearts by auricular contraction. He contends also that the crescendo quality of the murmur is not a characteristic of the murmur itself but depends upon an auditory deception (Gehörstäuschung) produced by its abrupt termination in the loud first sound.

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SYMPATHECTOMY IN THE TREATMENT OF ANGINA PECTORIS.

COMPARISON OF RESULTS WITH THOSE FROM PARAVERTEBRAL ALCOHOL INJECTION.

BY EDWARD P. RICHARDSON, M.D.,
AND
PAUL D. WHITE, M.D.,
BOSTON.

(From the Medical and Surgical Services of the Massachusetts General Hospital.)

Introduction. That painful stimuli arising in or near the heart may be modified by destructive interruption of pathways connecting with the central nervous system, has been clearly demonstrated. The treatment of angina pectoris by sympathectomy, suggested by François Franck[1] in 1899, and first carried out by Jonnesco[2] in 1916,

was given impetus in this country by Coffey and Brown[3] in 1923, who reported successful results from operations upon the left superior cervical ganglion only, rather than from the bilateral removal of the whole cervical sympathetic chain, including the first thoracic ganglia, as advocated by Jonnesco.[4] This substitution of a limited for a rather extensive operation led to an increase in the number of cases operated upon, and corresponded to a renewal of interest in the subject abroad. Consequently many cases of angina pectoris treated by operation, for the most part on the cervicothoracic sympathetic chain, have appeared in the literature, and have been summarized by Fontaine,[5] and more recently by Cutler.[6,7] In 1926, another development came when Swetlow[8] reported relief of pain by blocking the communications of this chain with the central nervous system by means of paravertebral injection of alcohol.

Although it may be conceded that the pain of angina pectoris can at times be relieved to a greater or less degree by these alternative procedures, operation or alcohol block, do these methods of treatment constitute good therapeusis, and if so, to what extent? This question may be answered only in part by the operative mortality and by the degree of relief immediately obtained. Further desirable criteria are the permanence of relief and in particular, the effect of operation on the duration of life, either through the interruption of the sympathetic innervation, or through the abolition of the symptom pain. Since interruption of the sensory stimuli probably does not alter the underlying pathology of angina pectoris, it has been suggested that the relief of the paroxysmal pain is harmful because thereby a warning symptom useful to the individual is done away with. On the other hand, it may be argued either that a reflex vascular spasm or a condition of shock excited by these stimuli is a cause of sudden death, or that the heart might be better for more exercise than the recurrent pain allows it. Such points may only be decided by following the clinical course of patients after treatment. Unfortunately, most of the reported cases have been published very shortly after operation. It is extraordinarily difficult to evaluate the indirect effects of operation in a symptom complex like angina pectoris, with a variable underlying pathology, a tendency to sudden accidents, and to spontaneous improvement. Under these circumstances, the place of radical therapeutic measures can only be gradually established through the accumulation of the late results of treatment.

Eight cases of angina pectoris were operated upon at the Massachusetts General Hospital between August, 1923, and December, 1926. Since the subject as a whole has been so admirably reviewed by Cutler,[6,7] the purpose of this paper is merely to present our own results of treatment, and the relative effects of operations which varied in extensiveness. Since February, 1927, paravertebral injec-

tion of 85 per cent alcohol, according to the method of Swetlow[8] has been used instead of operation. These injections were made by J. C. White and by W. J. Mixter,[9,10] and have been previously reported. An opportunity is thereby given to compare the effectiveness of operation and of paravertebral alcohol injection.

One important aspect of the subject is the selection of cases. While our impression of the type of cases suitable for these more radical forms of treatment will be given after a discussion of the results obtained, a few general considerations properly appear at this point. In the first place, there should be no question as to the diagnosis of angina pectoris, as distinguished from other forms of cardiac pain like that of coronary thrombosis or of effort syndrome. In any new treatment, the value of which is debatable, accuracy in diagnosis is peculiarly desirable. In some instances cited in the literature, operation has been performed upon patients in whom the diagnosis appears doubtful. Even the description of Jonnesco's[2] first case, cured for seven years, suggests paroxysmal tachycardia rather than angina pectoris. It should be further recognized that even if true angina exists, it is not incompatible with a considerable duration of life, or with attaining an age well beyond the average. By limitation of activity and particularly by avoiding conditions known to bring on attacks, patients may live for many years in relative comfort. In other cases, in spite of such care, and the relief obtainable through the use of the nitrites, the frequency and severity of attacks even during rest may be such that the suffering and disability are intolerable. Therefore, broad familiarity with cardiac conditions is necessary both for the diagnosis of angina pectoris and for the selection of cases for treatment by methods which still must be considered somewhat experimental. The occurrence of severe continuous pain due to coronary thrombosis is a contraindication to operative treatment, as is congestive failure, a development, moreover, ordinarily associated with the cessation of anginal attacks.

Since the extent of the removal of the cervicothoracic sympathetic chain varied in our cases, some anatomic discussion is necessary to correlate the clinical results secured with the degree of interruption of known pathways of conduction to and from the heart. The cervicothoracic sympathetic chain is principally efferent in function. It communicates with the central nervous system only through the rami communicantes of the thoracic nerves. Ransom[11] states that afferent impulses are carried from the plexus surrounding the heart, aorta, and coronary vessels to the spinal cord along the cardiac branches of the middle and inferior cervical sympathetic ganglia, the sympathetic trunk, white rami, and upper three or four thoracic nerves. The cervical sympathetic trunk above the middle ganglion, the superior cervical ganglion, and the superior cardiac nerve conduct efferent impulses only. The chief area of referred pain in angina pectoris is so clearly that of the cutaneous distribution of the

upper thoracic nerves that any conduction of painful sensations to the brain through the vagus must be of minor importance. We have had no experience with section, as recommended by Wenckebach,[12] of afferent vagus fibers, believed to form in man a separate depressor nerve, and carried out by certain surgeons, notably Eppinger and Hofer.[13] The function of this nerve in relation to angina pectoris as well as the chance of recognizing it at operation seem to us so doubtful as to make it an unpromising line of attack. On physiologic grounds, therefore, there are two points at which an effective block of sensory impulses passing through the sympathetic nervous system from the heart can be carried out. One is in the region of the inferior cervical and first thoracic ganglia, and is most simply accomplished by removal of these structures. The second is by interruption of the rami communicantes of the upper thoracic nerves. Division of the sympathetic trunk above the middle ganglion or of the superior cardiac branch, or removal of the superior cervical ganglion which interrupts both these structures, while breaking motor pathways to the heart, does not divide afferent fibers going to the spinal cord.

The operations, limited to the left side, carried out in the present series of cases were: (1) Removal of the superior cervical ganglion as recommended by Brown and Coffey;[14] (2) removal of the superior ganglion and sympathetic chain down to the level of the first thoracic ganglion; (3) removal of the inferior cervical and first thoracic ganglia, which form the stellate ganglion. Removal of the whole cervical chain including the first thoracic ganglion, the Jonnesco procedure, was not carried out in one stage in any case. The cases treated by operation[8] represent a small proportion of patients with angina pectoris (about 300) seen and followed during slightly over three years, and are presented herewith.

Case Reports. CASE I.—Male, aged forty-nine years, porter, entered the Massachusetts General Hospital on May 15, 1923, with the diagnosis of *syphilitic heart disease, aortitis, aortic regurgitation and angina pectoris*. The first attack of anginal pain occurred eighteen months before, and for thirteen months the attacks had been of increasing frequency. For three months he had been unable to work at all. For two months he had been treated in the out-patient department on account of this pain and a strongly positive Wassermann reaction with mercury and iodids, without benefit to the anginal attacks. The pain came on with exertion and sometimes after eating. It was usually in the region of the left second, third, fourth and fifth ribs, from the sternum to the anterior axillary line, agonizing and oppressive in character, sometimes radiating to the region of the left scapula, but not to the arm.

Examination showed the heart slightly enlarged to percussion and a to-and-fro murmur over the aortic area, with a water-hammer pulse. By Roentgen ray the aorta was a little prominent both to the right and left. The blood pressure was 112 systolic and 50 diastolic. The electrocardiogram showed a normal rhythm at a rate of 80. There was no evidence of congestive failure.

During rest in bed in the hospital he still had attacks of anginal pain, chiefly following meals, relieved by nitroglycerin. He was discharged in ten days, without essential benefit. He then remained quietly at home, but the attacks increased in frequency, so that he took 400 nitroglycerin tablets in three weeks. The attacks began slowly and could be aborted by nitroglycerin, but frequently occurred during complete rest.

He was readmitted for sympathectomy on August 14, 1923. Operation was performed on August 20 under ether anesthesia. The sympathetic cord on the left was removed from the inferior end of the superior ganglion to the superior end of the inferior ganglion. No middle ganglion could be recognized.

He made a good postoperative recovery. Horner's syndrome, narrowing of the palpebral fissure, with contraction of the pupil, occurred on the left. The attacks were relieved for three days, and then gradually recurred. The character of the pain was slightly modified, being located more definitely at the third left costochondral joint and was less agonizing in character.

After discharge on September 3, the attacks gradually increased in severity and in frequency up to thirty a day. The pain remained more definitely limited to the precordia. On October 18 he was readmitted for further operation.

Four days later the superior cervical ganglion was removed under ether anesthesia. Again the attacks ceased for two days, and gradually returned. After discharge they were more frequent than ever, occurring at all times of day or night, but still immediately relieved by nitroglycerin. The location, character and severity of the pain was not further modified by this second operation. He felt, however, that he had been improved and readily accepted the suggestion of further surgical treatment.

On November 24 the left inferior cervical and the first thoracic ganglia were removed under ether anesthesia. The operation proved somewhat difficult on account of adhesions from the previous operations, and from lack of the sympathetic trunk as a guide. The inferior cervical ganglion was found just internal to the vertebral artery, and continuous with the first dorsal ganglion which was behind and below the vessel. These structures were removed without appreciable effect on the patient.

Following operation, his general condition was satisfactory, but five hours later, during a vomiting attack, he stiffened convulsively, became cyanotic, and died within two or three minutes. There was no autopsy.

Comment. The operations in this case were limited in extent, in the hope of verifying what part of the sympathetic was most concerned in the transmission of impulses associated with angina pectoris. The sympathetic cord was removed first, since it was felt that thereby more afferent pathways would be severed than by the removal of the superior ganglion. While after this operation there was no theoretical reason why excision of the isolated ganglion should lead to further benefit, it was done as a test procedure. It produced no further observable effect. The effect of removal of the inferior cervical and first thoracic ganglia, from which much was hoped, could not be observed. The death of the patient seemed to be of cardiac nature. Subsequent cases were closely watched for forty-eight hours after operation, in order to give inhalation of amyl nitrite on the first sign of cardiac distress. This patient is classed as essentially unrelieved by his first two operations.

Case II.—Male, aged fifty years, laborer, entered the hospital October 25, 1923, after two weeks' observation in the cardiac clinic. About three months previously he began to have epigastric distress, radiating to the front of the left chest, and occasionally down the left arm. For two months it has been intense, and it left the patient weak and shaken. The attacks followed slight exertion, and occurred several times while at rest during the night. Nitroglycerin, at first effective, now failed to relieve the pain. He had been unable to work.

Examination was essentially negative aside from slight cardiac enlargement with evidence of peripheral arteriosclerosis. Roentgen ray showed the heart shadow enlarged to the left, the apex unusually blunt; there was no abnormality in size and shape of the aortic shadow. The electrocardiogram showed a normal rhythm, rate 70. The Wassermann reaction was negative; the blood pressure was 180 systolic and 90 diastolic. A diagnosis of *hypertensive and arteriosclerotic heart disease with angina pectoris* was made.

On November 7, 1923, removal of the left cervical sympathetic chain was carried out under ether anesthesia. The lower two-thirds of the superior ganglion, the sympathetic trunk, the middle ganglion, and the inferior cervical ganglion lying beside the vertebral artery were excised. The first thoracic ganglion was exposed but not removed.

Following operation, the patient had a cough and temperature reaction apparently due to a mild grade of bronchopneumonia. He had no more attacks of angina, but had occasionally a "warm" sensation over the precordia. Horner's syndrome occurred on the left, but there was no observable difference in the superficial circulation of the face.

On February 15, 1924, he reported himself symptomatically very much improved. He had had no pain at all, was able to walk for half an hour, and to carry coal up from the cellar. On exertion he sometimes had dyspnea and a sense of warmth at the second and third interspaces above the precordia.

On December 17, 1925, his family stated that he had returned to Poland in July, where he was working on a farm. Previously he had worked nine hours a day handling wet leather, and was able to walk a mile and a half to and from work. During this time he had some pain in his chest when he walked fast or overexerted himself, but he needed no medication.

On January 13, 1927, a letter from Poland stated that he was working on a farm, was very well and had no complaints.

At Christmas time, 1927, he continued to feel well except for some ill-defined leg-ache. There was little or no angina pectoris and no discomfort from the operation (cervical sympathectomy) that had been done over four years previously.

On August 11, 1928, the son reported that his father was well as far as his heart was concerned but complained of rheumatic pains in his legs. He was working on the farm in Poland. This was nearly five years since the operation.

Comment. The degree of benefit obtained for nearly five years in this case was very gratifying. While not entirely cured symptomatically, he was enabled to do manual labor, and was entirely satisfied with the result. We should class him as at least 90 per cent relieved.

Case III.—Male, aged fifty-three years, machine operator, entered the hospital on November 19, 1923. For two years he had had attacks of typical anginal pain, occurring over the precordia with radiation down the left arm. The attacks were associated with exertion, and occurred with

increasing frequency up to three or four times a day, causing him to give up work. His Wassermann reaction was strongly positive, and he had received a five months' course of antiluetic treatment, consisting of mercury, potassium iodid and neoarsphenamin, without benefit.

Examination showed his heart slightly enlarged to the left. A to-and-fro murmur loudest over the aortic area was heard. Roentgen ray confirmed the cardiac enlargement, and showed prominence of the aorta to the right and to the left. He was somewhat dyspneic, but showed no other evidence of congestive failure. The blood pressure was 146 systolic and 44 diastolic.

After a year's observation and treatment in the cardiac clinic of the outpatient department, he was sent in for sympathectomy, on account of his disability and lack of improvement, with a diagnosis of *aortitis (luetic), aortic insufficiency and angina pectoris.*

On November 21, 1923, the left sympathetic chain was removed to the level of the subclavian artery, including the superior ganglion, the sympathetic trunk, and the inferior ganglion. During convalescence he had no anginal attacks, and was discharged with the wound healed on the seventh day. Horner's syndrome was produced. After returning home the attacks recurred, and became more frequent and severe than before the operation. He died a cardiac death on July 6, 1924. There was no autopsy.

Comment. This patient showed temporary inhibition of attacks while in the hospital, perhaps as a result of anesthesia and rest, a phenomenon observed in other cases, and apparently having no significance with relation to permanence of relief. The operation, however, must be classed as completely ineffective in relieving the anginal pain.

CASE IV.—A male steward, aged thirty-seven years, came to the hospital on January 14, 1924, complaining of attacks of distress over the lower precordium of three years' duration. These attacks were brought on by exertion, and had a tendency to occur after meals, but also often awakened him at night. He would attempt to relieve them by standing up and taking long breaths, with an effort to belch. Twenty months previously on account of increase in frequency and severity, he consulted a physician who had his blood examined, said he had syphilis, and treated him by medication with some improvement until six months before admission. Then the pain became more severe and was brought on by very slight exertion. For the last three weeks he had been unable to work at all. The pain was most marked at the second interspace on the left and sometimes lasted as long as an hour, but was usually much shorter in duration.

Examination showed a thin, pale man, with a slow regular pulse. The heart was not enlarged to percussion. There was a roughening of the first sound at the apex, and a soft blowing diastolic murmur loudest over the aortic area. Blood pressure was 140 systolic and 50 diastolic. The Wassermann test was strongly positive. Roentgen ray showed some general enlargement of the heart but no increase in the supracardiac shadow. There was no evidence of congestive failure. The diagnosis was *luetic heart disease, with aortic regurgitation and angina pectoris.*

He remained on the medical wards for six weeks, having frequent attacks of substernal pain while in bed, especially at night, relieved by nitroglycerin. Mild antiluetic treatment seemed to increase rather than to relieve the pain. Accordingly sympathectomy was advised and carried out on March 3.

He became cyanotic under ether anesthesia although the quality of his pulse was good. The main sympathetic trunk was exposed and divided

1 inch above the inferior thyroid artery and the wound closed. After removal of the ether, the patient's color did not improve. He began to cough up pinkish froth, and died from pulmonary edema within twenty minutes, in spite of venesection and the administration of adrenalin, digifolin and atropin.

Comment. Death in this case was due to the effect of anesthesia on an incompetent heart. Section of the sympathetic cord undoubtedly had no effect on the outcome, which might easily have followed any minor operative procedure.

In view of the increasing number of cases in which good results were reported from removal of the left superior cervical ganglion alone, it was now decided to limit the operation to removal of this structure at a first stage, and if further operation seemed indicated to remove the inferior cervical and first thoracic ganglia. While ether had been chosen as an anesthetic, believing that through its similarity to alcohol and its vasodilator effect it would not provoke anginal crises, limiting operation to the superior ganglion had the advantage that it could readily be carried out under local anesthesia.

Case V.—A married Italian woman, aged twenty years, entered the hospital May 2, 1923, complaining of pain in the left arm and chest, shortness of breath and weakness. When she was six years of age she was ill for four months with rheumatic fever. During the next three or four years she had rheumatic attacks. From the age of ten until two years before admission she was well. Then she began to have pain in the left arm, dyspnea on exertion, palpitation and slight unproductive cough. She was in bed two months. Between September, 1921, and the date of entry she had three attacks of "cold" and "sore throat," with intensification of her symptoms. The pain in her left arm and left chest caused her to stop work.

Examination showed a well-developed and well-nourished young woman whose body was shaken by her cardiac pulsations. The heart was enlarged downward and to the left. There was a thrill over the aortic area, accompanied by a harsh systolic murmur. A softer diastolic murmur was heard all over the precordia. The blood pressure was 165 systolic and close to zero diastolic. There was no cyanosis. By Roentgen ray the heart was very much enlarged in all diameters. Electrocardiogram showed normal rhythm, rate 95, marked left axis deviation (index, + 42) and inverted *T* wave in Lead II. The diagnosis was *rheumatic heart disease, with aortic regurgitation and stenosis and mitral stenosis.*

She reëntered January 10, 1924, and remained for three months in the hospital. The attacks of pain were her chief complaint. This pain was sharp, knife-like, occurring over the precordia, and variably transmitted to the left back, axilla and arm. Examination was essentially the same as at the previous entry. There was no evidence of congestive failure. The pain was found to be associated with attacks of tachycardia. Quinidin was given without effect. Nitroglycerin relieved the pain.

Two years later, January 28, 1926, she came to the hospital, having been followed in the cardiac clinic. During this period she had done unexpectedly well, no congestive failure having occurred. The attacks of pain, however, had persisted and become more frequent. They were regularly relieved by nitroglycerin, of which she used nearly 200 tablets in a week and a half. Examination was essentially as before. It had become increasingly evident that the attacks of pain, at first attributed to paroxysmal tachycardia, were actually due to angina pectoris.

Since she was almost entirely incapacitated by the frequent attacks of pain, and had not otherwise lost ground to the extent expected, sympathectomy was thought advisable.

On February 2, 1926, the left superior cervical ganglion was removed under local anesthesia without incident. She was discharged twelve days later without having had any anginal attacks. The operation produced hyperesthesia of the side of the neck and face.

On April 1, 1926, her sister reported that following an attack of influenza she had had a recurrence of anginal pain, relieved by nitroglycerin.

On April 16, 1926, she was seen in the cardiac clinic. About one month before she had had an attack of respiratory infection during convalescence from which she began again to have typical angina pectoris always relieved by nitroglycerin. The attacks, however, were less frequent than before operation, requiring about two or three tablets daily.

In March, 1927, she developed bronchopneumonia at home and died after three or four days from the effects of the pneumonia itself. Prior to the infection she had been much improved as far as her heart and angina pectoris were concerned. There was no postmortem examination.

Comment. This case has been reported in detail.[15] While at first definitely benefited by operation, her attacks soon recurred. The period of relief seems too long to be attributed to the effect of anesthesia, and to the immediate psychologic effect of operation, and seems reasonably due to the sympathectomy, particularly since the angina pectoris when it did recur was much less severe than before operation. Ultimately her attacks of pain became infrequent and mild. No further surgical interference was carried out because of the patient's serious rheumatic heart disease, her respiratory infections, her dislike of further surgery and her gradual improvement. We would class her as 50 per cent relieved, for a period of one year up to her death from pneumonia.

Case VI.—A male laborer, aged fifty years, entered the hospital on May 18, 1925, complaining of pain in the left chest. Two months previously while working in a brickyard, he had a brief severe attack of pain over the precordium, which radiated to the back and down both arms. Three weeks before admission he was forced to give up work on account of the severity and frequency of similar attacks.

Examination revealed a vigorous looking muscular man. The heart showed a systolic murmur at the apex, but was not apparently enlarged; the supracardiac dullness seemed increased. His blood pressure was 140 systolic and 80 diastolic. The Wassermann test was strongly positive. Roentgen ray showed the heart shadow to be definitely enlarged, the supracardiac dullness increased, although in the oblique view the aorta did not appear to be enlarged. The appearance of the aorta was not characteristic of lues. Electrocardiogram showed normal rhythm, rate 65, left axis deviation.

In the hospital he developed a subdeltoid bursitis and was discharged June 4, 1925.

In the out-patient department he was treated with iodobismuthate of quinin, receiving 15 injections up to September 28, 1925. The attacks of angina pectoris nevertheless persisted and followed exertion, eating and sudden excitement. Nitroglycerin relieved the pain. He tried working for a few days, but had ten to fifteen attacks of pain a day, and was forced to keep quiet at home, where he still had four or five attacks a day. There had been no appreciable benefit from the antiluetic treatment.

On November 2, 1925, he was readmitted to the hospital. The physical examination was essentially the same as at the first entry. The diagnosis was *angina pectoris, tertiary syphilis.*

On November 6, the left superior cervical ganglion was removed under novocain, which had to be supplemented by ether. Until his discharge two weeks later, he was much improved, having, however, occasional mild attacks of pain which did not require nitroglycerin. Following operation, he had pain in the left side of the face on eating, and pain in the left shoulder, which appeared to be due to an intensification of his previous subdeltoid bursitis, but may have been dependent on postoperative hyperesthesia. Horner's syndrome was produced.

Following discharge, the attacks recurred in their previous frequency and severity. The pain in his shoulder and face was extremely troublesome. He was still completely incapacitated. During the interval, he had 8 injections of neoarsphenamin.

On February 1, 1926, he reëntered for further operation which was done twelve days later. The aorta was now found enlarged by Roentgen ray in the oblique view and the findings were more characteristic of syphilitic aortitis. On February 12, 1926, under ether anesthesia the sympathetic trunk was picked up on the left where it formed a loop around the inferior thyroid artery, and followed downward, exposing two ganglia, the lower of which, about 1 by 1.75 cm. in size, lay behind the subclavian artery below the origin of the vertebral artery. These ganglia were identified as the inferior cervical and first thoracic ganglia, and were completely removed. During the operation a small opening was made in the thoracic duct.

On the day following operation, anginal attacks occurred, and persisted irregularly through convalescence, once or twice daily, usually waking him from sleep. The pain was precordial, radiating to the left arm, hand, shoulder and scapular region, and also to the left occiput and parotid region. It was relieved by nitroglycerin. The wound healed promptly in spite of injury to the thoracic duct. During convalescence the blood pressure was essentially equal in both arms.

Following operation he reported regularly to the cardiac clinic. The anginal pain occurred as before, and hyperesthesia and pain in his shoulder and also pain in the region of the left lower jaw were extremely troublesome. Between March 25 and May 13, he received 8 injections of neoarsphenamin.

On May 20, 1926, he was not doing well. The pain was substernal, with radiation to both arms.

On June 16, he continued to have attacks of substernal pain. He was unable to work and took several nitroglycerin tablets daily.

On July 8, he was considerably improved; he used about two nitroglycerin tablets daily, and wanted to try some light work.

On August 5, he was getting on fairly well, working nine hours a day loading brick. He still had some angina pectoris, and took two tablets of nitroglycerin daily.

On November 18, 1926, he was feeling better, working three or four days a week handling bricks.

On March 24, 1927, he had been laid off from work since Christmas because of slack business. He felt much better on the whole. There were still attacks of pain, starting midsternally, and radiating down the right arm, usually after eating. He took four to six tablets of nitroglycerin a week. His left hand had been cold since operation. The pain in the left jaw was still present on beginning to eat, but was better. The pain in the left arm and shoulder was all gone. He did not sweat on the left side of the face or in the left arm. He had no disability with his arms on working. The pain in the precordia was less frequent and less severe. When it came it radiated to his right arm and somewhat to the left side of the neck. On examination the left arm and hand were colder than the right.

On February 2, 1928, he reported again. He had worked at intervals at bricklaying. He used two nitroglycerin tablets a day when working, one a week when not. Examination was as previously, fluoroscopy showing a slight aortic dilatation, and slight cardiac enlargement. Horner's syndrome continued.

On May 14, 1928, further antiluetic treatment was advised. There was no change in his symptoms or physical examination from those noted in February, 1928.

On August 16, he was still at work in the brickyard, taking two nitroglycerin tablets daily.

Comment. This case was undoubtedly benefited by the treatment. Whether the improvement should be attributed to operation or to antiluetic treatment is doubtful. We are inclined to believe that the operation had a greater effect than the drug therapy although it certainly was only partially successful.

Pain in the shoulder and jaw in this case was extremely troublesome following operation. However, it eventually disappeared. It is of interest in connection with ischemic conditions of the extremities that the later effect of removal of the stellate ganglion was vasoconstriction rather than vasodilatation. We should class this case as 60 per cent improved.

CASE VII.—A garage owner, aged fifty-nine years, was referred to us in consultation in May, 1926, by Dr. W. A. Putnam of Cambridge, for substernal distress of twelve years' duration, at first only with heavy work or lifting, but then brought on by the least exertion. The pain was substernal and precordial, radiating to the left shoulder, the left arm and left back, extending to the throat somewhat, but not to the face or jaw. The pain was brought on by walking or excitement, but not by meals. It was always relieved by nitroglycerin. Since April he had been unable to work, and the attacks were growing progressively more severe, and were brought on more easily. His past history was not remarkable.

In October, 1926, he was seen again and was no better and operation was thought advisable.

Examination showed a man somewhat overweight, but appearing in good health. His heart was regular in action, and negative to auscultation and percussion. His blood pressure was 135 systolic and 90 diastolic; the urine and Wassermann tests were negative. The diagnosis was *arteriosclerotic heart disease, angina pectoris.*

On October 18, 1926, the left superior cervical sympathetic ganglion was removed under local anesthesia without incident. Horner's syndrome was produced. During the same morning he had an anginal attack, and others occurred on the fifth, sixth and seventh days. The pain was located somewhat more externally, nearer the axilla, but was similar in severity. He also complained of pain in the region of the left jaw, on beginning to eat. He was discharged on the seventh day.

On November 3, 1926, the attacks were the same as before operation in frequency and severity.

On December 9, 1926, he died after an attack of pain lasting twelve hours, believed to be due to coronary thrombosis. There was no autopsy.

Comment. Operation was totally ineffective in this case. It is very improbable that it was in any way responsible for the coronary thrombosis which occurred seven weeks later.

Case VIII.—A traveling salesman, aged fifty-nine years, was referred to us by Dr. W. A. Putman, December 8, 1926. Six months before he had begun to have slight substernal distress, which was benefited by a month's vacation. On return to work, which involved the carrying of heavy sample cases, the pain became much worse, so that he had done nothing for two months, and during the last two weeks he had been in bed. The attacks ordinarily came on with exertion, but he had had two or three daily while in bed. The pain was relieved by nitroglycerin, of which he was taking 100 tablets a week, and was located under the lower end of the sternum, in the median line, extending outward on both sides equally, and upward to the sternal notch. It was also felt in the left wrist. His health was otherwise good, and his past history without significance; there had been no venereal disease.

Examination showed a florid man, weighing about 215 pounds. His pulse was regular, his heart negative to auscultation and percussion, except for slight cardiac enlargement. Blood pressure was 155 systolic and 90 diastolic. The urine was normal. *A diagnosis of angina pectoris* was made.

On December 13, 1926, his left superior cervical ganglion was removed under local anesthesia. He made a good convalescence, without definite anginal attacks, and was discharged on the seventh day.

On April 28, 1927, he reported that he had felt distinctly improved by the operation, and had resumed work. He was able to walk several miles a day. He had had only one attack at night, but sometimes took one or two tablets a day and sometimes none at all.

The pain when it occurred was bearable. He now felt it first to the right of the sternum, along the fourth costal cartilage. His left eyelid drooped rather conspicuously, but he had no difficulty with his eyesight. He had had pain under the left jaw on beginning to eat, sometimes mild, sometimes severe. The skin was not hyperesthetic.

On May 11, 1928, the patient wrote that he felt perfectly well and had had no pain for many months. He had not taken any nitroglycerin tablets since August, 1927. He was working every day, and carried sample rolls when necessary. He was able to bowl with large balls and did anything he ever did, except to run for a train.

Comment. We should class him as 100 per cent relieved when last heard from. Why the late result should be better than the immediate effect of operation in this case is not at all clear. It is possible that some of the relief may have been a spontaneous recovery although the chief responsibility for his improvement must rest with the operation.

Discussion. Among 8 cases having 11 operations, there were 2 operative deaths, a mortality rate of 25 per cent of cases, and 19 per cent of operations. This death rate might have been reduced by a better selection of anesthesia. Cutler[6] found the immediate mortality of sympathectomy in 120 collected cases of angina pectoris to be 5.8 per cent. In our series, lasting benefit followed operation in 4 cases, and was directly attributable to it in 3. In only 1 case out of 5 did satisfactory relief follow removal of the left superior cervical ganglion alone, although another (Case V) was considerably improved. In the other 2 patients benefited (Cases II and VI), afferent connections from the heart must have been severed to a greater or less extent (Table I).

TABLE I.—CASES TREATED BY SYMPATHECTOMY AT THE MASSACHUSETTS GENERAL HOSPITAL.

Operation.	Deaths.	Failures.	Lasting improvement.
Removal of superior ganglion, Cases I, V, VI, VII, VIII	0	3	2 (Case V, 50 per cent) (Case VIII, 100 per cent)
Removal of cervical sympathetic chain, Cases II, III	0	1	1 (Case II, 90 per cent)
Removal of inferior cervical and first thoracic ganglia, Cases I, VI	1	0	1 (Case VI, 60 per cent)
Incomplete Operation, Case IV	1		
	2	4	4

During the course of operation, no constant effect on the blood pressure or pulse rate was noted as a result of manipulation of the sympathetic chain. The excitement and mental strain of going through operation, even under local anesthesia, did not in any case precipitate an anginal attack. Horner's syndrome was regularly produced but there was no obvious change in the superficial circulation of the face. The blood pressure in the two arms was approximately equal, even in the case surviving removal of the stellate ganglion.

The fleeting cessation of attacks of pain following operation was interesting, and seemed more definite in patients receiving ether anesthesia than in those operated on under novocain. It shows that relief of pain immediately following operation should not be attributed in all cases to nerve section.

Pain in the region of the left jaw on beginning to eat was present in half the cases, but was troublesome rather than serious. Painful hyperesthesia occurred less frequently, and was distressing in only 1 patient (Case VI). Such after effects tended to disappear with time. These patients have apparently been little conscious of the change in the left eye. There was an occasional complaint of the lid drooping, or of the eye watering in the wind.

If the cases are grouped on a probable etiologic basis, there are 4 syphilitic cases, I, III, IV and VI. Of these, 2 died following operation, 1 was totally unrelieved, and 1, Case VI, was eventually partially relieved and enabled to work, but his improvement occurred so long after operation that some doubt must remain whether it was due to his operation or to further antiluetic treatment. This patient is the only one of the syphilitic group still alive, thirty-three months after his first operation.

Of 3 cases, II, VII, VIII, arteriosclerotic in origin, 2 were alive and greatly relieved, 1 after fifty-seven months, and the other after seventeen months. One case died seven weeks after operation, apparently of coronary thrombosis.

In 1 rheumatic case, Case V, the relief (50 per cent) obtained from

removal of the left superior ganglion was perhaps hardly enough to justify the operative discomfort and risk.

While these cases are too few in number to draw general conclusions, it would nevertheless suggest that syphilitic cases are poorer risks for operation, and also that the relief obtained may be less than in cases with an arteriosclerotic basis for their symptoms. Or, if we include Case V, it is possible that anginal pain, associated with dilatation of the aorta or with aortic regurgitation, may be less amenable to relief through sympathectomy than when occurring without this complication.

On considering these results early in 1927, we were on the whole not greatly encouraged in continuing with sympathectomy in angina pectoris. While relief had been occasionally obtained it had been at the expense of too great risk to the patient. We were particularly disappointed in the effect of removal of the superior cervical ganglion only, from which good results had been reported in the literature. The by-effects of operation, eye changes and hyperesthesia, did not greatly influence us, since the patients, unintellectual it is true for the most part, did not complain of their eye trouble, and the painful hyperesthesia tended to wear away. But it made a great difference whether removal of the superior ganglion alone, which could usually be done with care under local anesthesia, was effective, or whether it was necessary to remove the inferior cervical and first thoracic ganglia, a much more considerable procedure.

Our feeling was that the removal of the left superior ganglion only was in our hands too uncertain in its effect on pain to be recommended. More definite benefit should be obtained to justify the operative risk. When the sympathetic chain is exposed through an adequate incision, it is not difficult to remove it all, including the first thoracic ganglion. Opinions differ as to the effect of this procedure. Danielopolu[16] believes that the operation intercepts the cardiac accelerator fibers and the cardiac and pulmonary vasomotor nerves, and that excision of the first thoracic ganglion seriously affects the physiology of the myocardium. The opinion of Leriche's Clinic, as expressed by Fontaine,[5] is that after removal of the stellate ganglion, the heart will be adequate for its usual work, which it regulates, thanks to its intracardiac nervous apparatus, but it will be unable to accommodate itself to abnormal conditions, whether created by excessive work or by pathologic processes. These authors have suggested operations planned to sever only the sensory connections of the heart. But fears as to the competence of the heart have hardly been borne out by clinical experience. On the experimental side, Cutler[7] states that dogs in whom the cervical sympathetic chain and stellate ganglia have been eradicated showed that their activity, well-being and response to exercise were equal to control animals. Cannon's[17] experience with animals having complete sympathetic denervation does not suggest harmful effects from interruption of sympathetic control in man.

We were considering, therefore, the advisability of a more extensive removal of the sympathetic connection of the heart as a primary procedure. In this we feared not so much the ultimate physiologic effect of the operation as the immediate dangers of a somewhat extensive dissection requiring general anesthesia and displacement of the great vessels at the root of the neck in patients who are as a class bad risks. As an alternative means of treatment, it was decided to try the effects of paravertebral injection of alcohol as advocated by Swetlow.[8] The results obtained have been reported by J. C. White and P. D. White,[9] and by W. J. Mixter and J. C. White,[10] and will be briefly summarized here for the sake of comparison.*

Altogether 8 cases have been treated by this means, 2 of them receiving two injections. The results obtained are summarized in Table II. These cases as a whole are comparable in seriousness to those treated by operation; the patients were either incapacitated or bedridden on account of the severity and frequency of their attacks. Three of them had coronary thrombosis and so would not have been suitable risks for operation; they survived the paravertebral alcohol injection without difficulty.

The point of attack in paravertebral injections of alcohol, the rami communicantes of the upper thoracic nerves, is anatomically sound with regard to interruption of the afferent impulses from the heart. The method has the obvious disadvantages of any blind destructive procedure, in particular the possibility of injury of the spinal cord by diffusion or misplaced injection. Special skill and experience is naturally required. We can only say that no lasting ill effects have as yet occurred. In 2 cases, rather alarming immediate effects were observed; in 1 a considerable fall in blood pressure, in another severe pain presumably from pleural irritation. Against these possibilities must be balanced the mortality of sympathectomy. With regard to relatively minor disadvantages, Horner's syndrome also follows paravertebral injection, particularly in successful cases. Regional hyperesthesia, although more constantly produced, appears less lasting than after sympathectomy. From this point of view, there is apparently little choice. The shorter hospital stay required following injection is a slight advantage. Injection so far as the experience of this clinic goes, has the definite advantage of being a safer procecure.

Symptomatic relief has more constantly been secured by paravertebral injections than by operation in our series of cases. While there has been a tendency for pain to recur in 1 or 2 cases, the relief has generally lasted as long as the patients have been followed, up to eighteen months in 1 case. Against this possibility of recurrence may be set the possibility of repeating the treatment when necessary.

* We are very grateful to Dr. J. C. White and Dr. W. J. Mixter for permission to include their material in this paper.

TABLE II.—CASES TREATED BY PARAVERTEBRAL ALCOHOL INJECTIONS AT THE MASSACHUSETTS GENERAL HOSPITAL.

Case.	Diagnosis.	Age, sex.	Treatments.	Result.	Degree relieved.	Duration.	Status at last report.
I (E. M.)	Syphilitic aortitis, aortic regurgitation, hypertension, angina pectoris; confined to bed	54 M.	Left 2/19/27; right 3/20/28	Left-sided relief; development of right-sided pain; no relief	100 per cent (left side) 0 per cent (right side)	To date	Up and about July, 1928, but unable to work; moderate attacks of right-sided pain.
II (H. T.)	Hypertensive and arteriosclerotic heart disease; aortic regurgitation, angina pectoris; previous attack of coronary occlusion; slight congestive failure	60 M.	Left 5/16/27; reinjection 6/23/27	Considerably relieved; further relief	50 per cent	To death	Able to resume light work; until sudden death, undoubtedly from coronary thrombosis or angina pectoris February 8, 1928; no autopsy.
III (M. K.)	Arteriosclerotic heart disease; hypertension; angina pectoris at rest	53 F.	Left 6/9/27	Relief slight but definite; difficult to judge because of extreme nervousness	20 per cent	To date	Up and about, quietly active, appearing in good health but with moderate angina pectoris, July, 1928.
IV (S. F. B.)	Moderate arteriosclerosis and enlarged heart; angina pectoris; incapacitated	54 M.	Left 7/22/27	Left-sided relief; mild right-sided attacks	100 per cent (left side)	To date	In fair health, June, 1928, but still has right-sided angina pectoris; has resumed work as truck driver.
V (E. C.)	Arteriosclerotic heart disease; hypertension; myocardial insufficiency; previous coronary thrombosis	59 M.	Left 8/12/27	Relief partial	25 per cent	To death	Died suddenly, January 9, 1928, undoubtedly of coronary thrombosis or angina pectoris; no autopsy.
VI (H. C.)	Hypertensive heart disease; aortic regurgitation; angina pectoris at rest	52 M.	Left 11/5/27	Complete relief at first (few months); later slight recurrence	100 per cent 90 per cent	To date	Comfortable and able to do light work, August 1, 1928.
VII (L. A.)	Arteriosclerotic heart disease; hypertension, angina pectoris	58 M.	Right 3/3/28	Considerable relief	65 per cent	To date	Fairly comfortable and has resumed light work, August, 1928.
VIII (C. Y.)	Arteriosclerotic heart disease; hypertension; angina pectoris; previous coronary thrombosis	68 M.	Left 4/17/28	Partial relief at first, then recurrence; judgment of case somewhat difficult because of much nervousness	75 per cent 50 per cent	To date	Uncomfortable, angina pectoris daily but able to be quietly up and about, July, 1928.

In 2 cases, classed as 100 per cent relieved, this benefit applied only to the side first injected. They continued to have right-sided attacks, milder in nature, and consequently were not so completely relieved as the 2 best cases following operation (Cases II and VIII).

In only 1 instance, did injection (Case VI) secure as good a general result as in the 2 operated Cases II and VIII.

Treatment of anginal pain by paravertebral alcohol injection we believe, therefore, at present to be superior to sympathectomy. No case has been treated by operation here since the injections were first tried. Whether or not a return to direct operative methods will be made as a supplementary procedure under special indications cannot as yet be said. At least we have not tried the combination.

The broad question remains as to whether any good has been accomplished by these destructive measures. We feel on the whole that there has been benefit, in spite of the two operative fatalities. Suffering has been relieved, bedridden patients have been restored to activity, and a few individuals, operated Cases II, VI and VIII and injected Cases IV, VI and VII, have been returned to economic usefulness. Nor can it be said definitely that this has been at the expense of further damage to the circulatory apparatus, or of harmful overexertion, due to absence of the warning pain. While deaths have occurred some months after operation, it is not clear that those patients who survived treatment have been more subject to accidents congestive failure, coronary thrombosis, or sudden fatality, than might be expected in a group of equally severe anginal cases treated conservatively.* We believe that treatment by paravertebral injection is justifiable in carefully selected patients who do not respond to other forms of treatment.

The selection of cases, therefore, is the most important aspect of the situation. It may be summarized as follows: Paravertebral alcohol injection, generally of the left upper five thoracic nerve roots, may be recommended in the treatment of obstinate angina pectoris which persists in spite of ample medical measures, and which renders work impossible and life miserable. Given these indications there seem to be no contraindications. The injections may be made even after coronary thrombosis, and doubtless are much less of a risk than is cervical sympathectomy. It is quite possible that failure of a paravertebral alcohol injection may justify operative procedures but our experience to date would indicate that the therapy of first choice for angina pectoris when medical measures have failed is the injection method.

* We have seen one case, however, operated elsewhere (left cervical sympathectomy) with almost complete (95 per cent) abolition of the angina pectoris, who undoubtedly was too active as the result of his freedom from pain and who died from congestive failure six months after the operation. How much longer he would have lived had he remained very quiet or whether his angina pectoris would have killed him sooner had he not been operated are questions which must remain unanswered.

Conclusions. (1) The pain of angina pectoris may be modified or abolished by operation on the cervicothoracic sympathetic system, or by paravertebral injection of alcohol.

2. That the relief of pain or interruption of the nervous mechanism of the heart exerts a harmful effect on the course of the disease, although possible, is not proved.

3. Paravertebral injection of alcohol appears safer than operation upon the sympathetic connections of the heart in the treatment of angina pectoris.

4. In carefully selected cases, refractory to other measures, further observations on the effect of paravertebral injections of alcohol are justified.

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THE SYMPTOM OF SIGHING IN CARDIOVASCULAR DIAGNOSIS.*† WITH SPIROGRAPHIC OBSERVATIONS.

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For the diagnosis of effort syndrome, neurocirculatory asthenia, cardiac neurosis, nervousness and fatigue the symptom of sighing is a useful but much neglected aid, especially in differentiating these conditions from disability due to cardiovascular disease. Its very frequency and simplicity have doubtless led to its neglect. About five years ago our attention was attracted to the value of observation and inquiry of the frequency and degree of sighing and for the last two years the symptom has been routinely looked and asked for in the examination of patients. On several occasions, indeed, we have even been asked to see in consultation patients whose only symptom or sign was constant sighing. Because of the scarcity of data on sighing and of the lack of knowledge of its application to internal medicine, we have made a study of it from certain points of view during the past year, especially as to its place in cardiovascular diagnosis. It is this study that we are reporting here.

A sigh (Latin, suspirium) is best defined as follows (Webster's Dictionary, 1924) "A single, deep, prolonged, audible respiration, especially as the involuntary expression of fatigue, exhaustion, grief, sorrow, or pleasure."

We have searched many of the best known authoritative medical works, past and present, especially those dealing with the heart, and but rarely have we found any reference, even in passing, to this interesting symptom. Graham Steell[1] and Crummer[2] have written of it briefly as follows. Steell,[1] in 1906, said "A peculiar and also rare variety of dyspnea—if such it can be called—is that which causes the patient in repose to take occasionally a very deep breath or 'sigh.' This occurrence was described many years ago, and was then associated with fatty degeneration of the heart muscle. The patient is hardly aware of any feeling of dyspnea, and the long drawn breath is largely automatic, but there is probably generally some slight subjective sensation of 'air hunger'." Crummer,[2] in

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† Fourth of a series of papers from the Massachusetts General Hospital on Clinical Spirography.

1925, said "Dyspnea of purely nervous origin may be experienced as a thoroughly disagreeable sensation by such patients. Two simple types of nervous dyspnea may be recognized. In the first, a sighing respiration occasionally interrupts the sequence of breathing and is preceded in the patient's consciousness by a sensation amounting to air hunger. In the second, there are periods of increased rapidity with shallow breathing, which is aptly described by the word panting."

It has been our experience, both before and during the special study to be recounted here, that whereas dyspnea, palpitation, and heart pain may be due either to heart disease or to fatigue or nervousness, sighing is never due primarily to heart disease but always to fatigue or nervousness or other such factor. Thus it is at times of great value as a symptom in the differential diagnosis of cardiovascular disease, and along with dizziness, faintness and tremor helps to diagnose effort syndrome. Even when heart disease has been found to be present the symptom of sighing aids much in the determination of the percentage of responsibility of heart and nervous system in the production of disability in a given case.

As we already have said, sighing is frequent. Nearly everyone sighs at times under certain provocation. Also it may be a habit in a few people, even in earliest childhood. The degree and frequency of sighing in a given individual, and not its mere existence, are what determine its importance as a symptom, just as thirst and drowsiness, if excessive, may become important symptoms of disease.

Present Study. The first part of our study of sighing has included observation and inquiry of its frequency in 650 people, mostly adults, of whom 400 were normal controls, nearly all young men and women, 100 were cases of organic heart disease who were not especially nervous or tired (half of whom had congestive failure and half had not), 100 were cases of nervous fatigue or effort syndrome without heart disease, and 50 were cases with both organic heart disease and effort syndrome.

The second part of our study has concerned itself with graphic records of the respiration (spirograms) taken to determine the frequency of sighing, or reviewed when taken in the past to determine the condition of the cases who showed increased sighing. The spirograms were obtained as in the routine method of determining the basal metabolic rate.

We have used as a criterion of frequent sighing a lower limit of at least ten respirations on the spirogram which were 50 per cent or more deeper than the usual respirations in the course of ten minutes, or at least five respirations twice as great or more than the usual in this same interval of time. Many normal people show one or two increased respirations in the course of ten minutes, but many more show no increase at all. There are borderline cases but we

have set the limit sufficiently above the usual normal to be very significant.

Thirteen of the cases of organic heart disease without nervous fatigue were traced in this way, 8 of those with congestive failure and 5 without; 8 of the cases of effort syndrome were so traced; graphic records were also made from 12 of the control cases without either heart disease or effort syndrome, and from 8 of the group of combined heart disease and effort syndrome. Thus 41 cases from all four groups were traced. Two hundred spirograms already taken in the past were reviewed to determine the diagnoses in cases showing well-marked sighing. Ten cases of hyperthyroidism and 10 of hypothyroidism were studied also by graphic record. Finally, the state of the blood gases was studied in 2 of the cases showing much sighing.

Results of Study. I. *Statistics.* Four hundred healthy adults without heart disease were asked about the frequency with which they sighed. Fifty did not know whether they sighed or not, 42 said that they did not sigh, 77 that they sighed rarely and 155 that they sighed occasionally. Seventy-six, or 19 per cent, stated that they sighed frequently.

Sixty of these 400 control cases were school boys, fifteen to nineteen years; 9 of them (15 per cent) sighed frequently. One hundred and six were young men studying medicine, twenty-one to twenty-nine years of age; 11 of them (10 per cent) sighed frequently. One hundred and eighteen were school girls fifteen to twenty years of age; 20 of them (17 per cent) sighed frequently. One hundred and eight were young women in college, eighteen to thirty-two years of age; 36 of them (33 per cent) sighed frequently. Evidently under ordinary conditions, therefore, young women in the third decade of life are likely to sigh often. Mitral stenosis in such individuals should not be wrongly blamed for this natural tendency to nervous and cardiovascular symptoms. The causes cited, in the order of their frequency, which were thought responsible by these control cases for their sighing were mental fatigue, physicial or mental fatigue or both, "unknown" depression, relief, disgust, disagreeable tasks, physical fatigue, worry, emotional distress, exasperation, overeating, disappointment, boredom, insufficient sleep, unhappiness, examinations, and long lectures.

Of 100 patients with organic heart disease with and without congestive failure who were not nervous, 24 were found to sigh, but the symptom was a frequent one in only 3 (3 per cent), 2 of whom were young females without congestive failure and the other one a middle-aged man with congestive failure.

Of 100 patients with effort syndrome, nervous fatigue, or excessive nervousness, without heart disease, all but 9 stated that they sighed and the sighing was frequent in 80 (80 per cent), of whom

51 were women, 33 under the age of forty years. Four of the effort syndrome cases, one girl aged fourteen years, one boy aged fourteen years, and two men, one young and one middle-aged sighed excessively, the symptom of sighing being the chief complaint.

Finally of 50 cases of heart disease and effort syndrome combined only 3 denied sighing, while in 37 (74 per cent) it was a frequent occurrence. Thirty-seven of the 50 cases were women and 29 of them sighed often (78 per cent); 13 were men and 8 of them sighed frequently (62 per cent). All ages were represented. In 2 cases

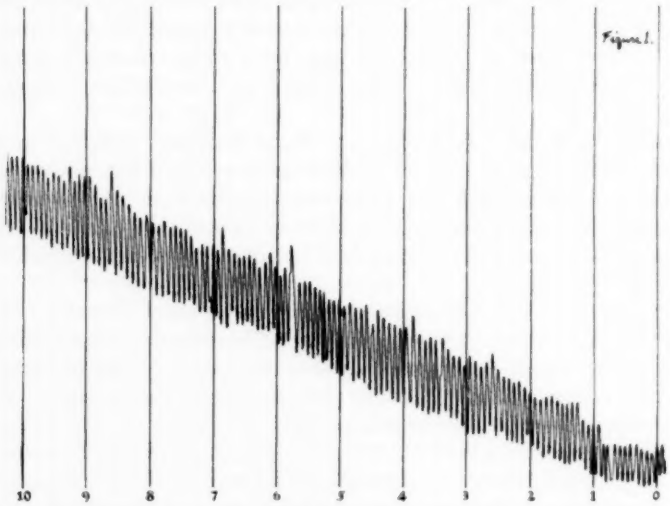

FIG. 1.—Respiratory tracing from a young woman with organic heart disease (mitral stenosis) without congestive failure or nervousness. As in the remaining figures, the tracing reads from right to left and the time intervals mark off minutes. No deep respirations or sighs are present in this tracing although a few breaths are a little fuller than the others. The respiratory rate is 12 per minute. The tracing covers a ten-minute period.

(females one young and one middle-aged) sighing was the chief complaint. In almost all of these 50 cases the nervous factor was much more responsible than the cardiac factor for any disability present.

II. *Respiratory Tracings.* Respiratory tracings were taken for intervals of ten minutes from 41 cases respresenting all four groups: (1) Control cases without either heart disease or effort syndrome; (2) cases of organic heart disease without nervousness or effort syndrome; (3) cases of effort syndrome without heart disease, and (4) cases of heart disease and marked nervousness or effort syndrome. These tracings fully confirmed the statistical data.

Of the 5 cases with organic heart disease without effort syndrome or congestive failure who were traced, none showed abnormal sighing (0 per cent). A typical example is given in Fig. 1.

Of the 8 cases with organic heart disease without effort syndrome but with congestive failure, none showed abnormal sighing (0 per cent). Typical examples are given in Figs. 2 and 3. This finding is especially significant because all these patients were suffering from dyspnea, distressing in several and Cheyne-Stokes in character in one.

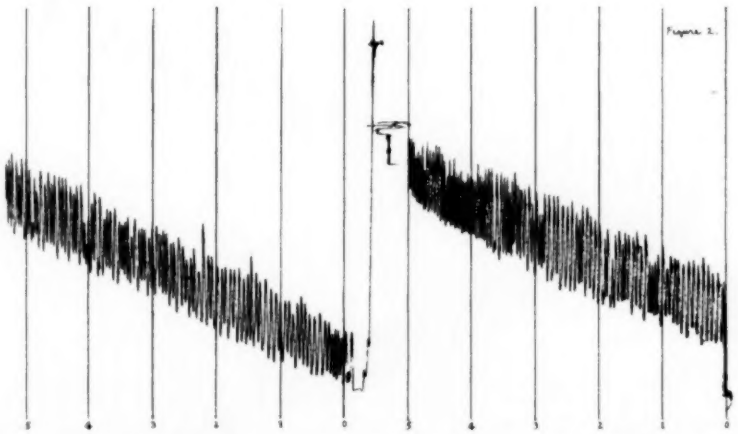

FIG. 2.—Respiratory tracing from a middle-aged woman with organic heart disease (hypertensive, arteriosclerotic type) with congestive failure. After the first period of five minutes dyspnea became so marked that the tracing was stopped for a rest period, and this was followed shortly by a second five-minute tracing. The respiratory rate increased in each of the strips of tracing, from 13 to 26 per minute in the first and from 15 to 19 in the second. In spite of the dyspnea no sighing respirations occurred.

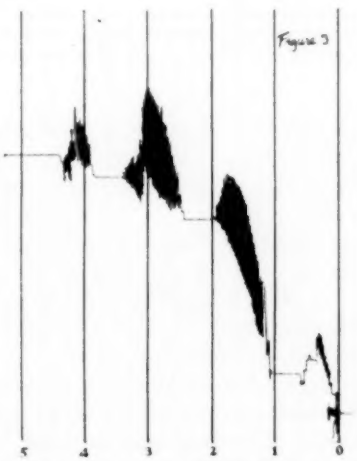

FIG. 3.—Respiratory tracing from an elderly man with organic heart disease (hypertensive-arteriosclerotic type, with auricular fibrillation) showing congestive failure and Cheyne-Stokes respiration. A period of five minutes is represented with four cycles of hyperpnea and apnea. No sighs occurred.

Of the 8 cases with effort syndrome or marked nervousness without organic heart disease, 6 showed abnormal sighing (75 per cent). Typical examples are given in Figs. 4 and 5.

Of the 8 cases with both effort syndrome or marked nervousness and heart disease 6 showed abnormal sighing (75 per cent). A typical example is given in Fig. 6.

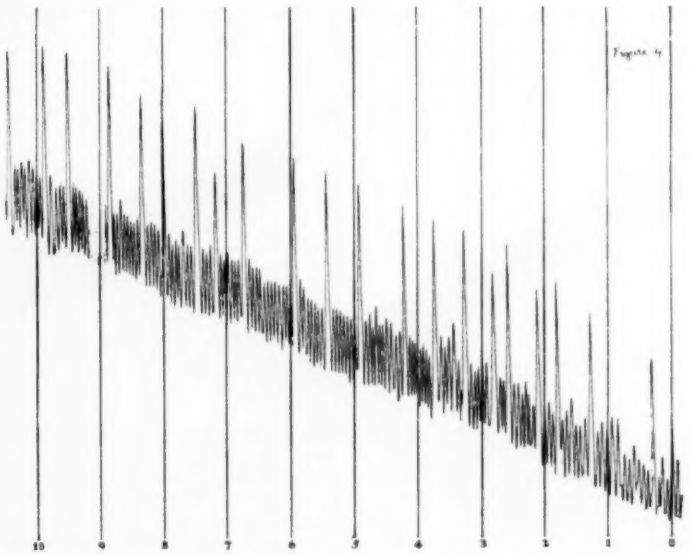

FIG. 4.—Respiratory tracing from patient (a middle-aged woman) with effort syndrome and marked nervousness without heart disease. In the period of ten minutes twenty deep prolonged respirations (sighs) occurred. The respiratory rate varied from 13 to 16 per minute. Total ventilation was somewhat increased above the average.

Of the 12 control cases without either heart disease or effort syndrome or marked nervousness who were traced none showed abnormal sighing (0 per cent). Typical examples are given in Figs. 7 and 8.

After these groups had been studied and their spirograms obtained, 200 routine unselected respiratory tracings on file in the Metabolism Laboratory at the Massachusetts General Hospital were examined, with the kind permission of Drs. Means and Thompson and the assistance of Miss Hardy.

Of these 200 tracings, 35 were found to show an abnormal degree of respiratory irregularity in accord with the criteria of abnormal sighing already noted. The diagnoses in these 35 cases were found to be psychoneurosis in 5, hyperthyroidism in 5, pituitary disease in 3, nontoxic thyroid adenoma in 2, and scattered in the remainder. The scattered diagnoses included neurasthenia, visceroptosis,

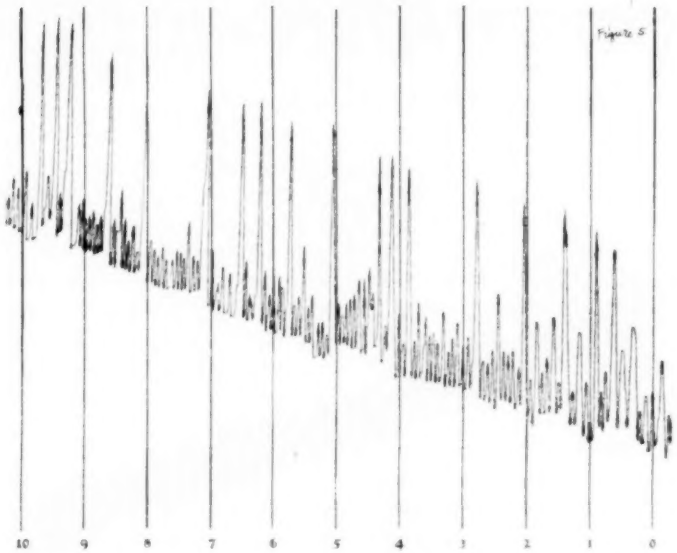

FIG. 5.—Respiratory tracing from a girl, aged sixteen years with marked effort syndrome and no heart disease. She had been seen in consultation because of the chief complaint of constant and marked sighing. No disease was found after careful study in the hospital. In the period of ten minutes 24 sighing respirations occurred. The respiratory rate was somewhat irregular, varying from 8 to 13. Many of the breaths were very small, compensating for the deep respirations, so that the total ventilation was within normal limits, averaging 8.6 liters per minute.

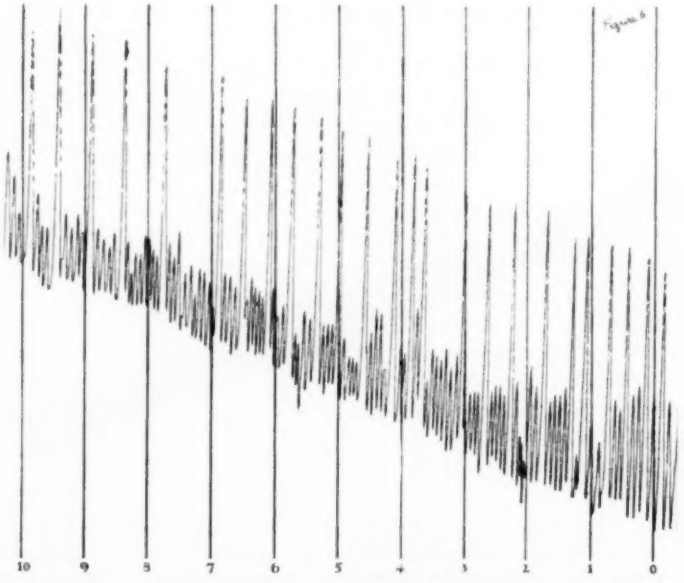

FIG. 6.—Respiratory tracing from a young woman with both heart disease (rheumatic aortic regurgitation) and marked nervousness. Note the large number of deep respirations (sighs), a total of 24 in ten minutes. The respiratory rate varied from 9 to 13 per minute.

poor posture, endocrine disorders, obesity, chronic arthritis, and so on. It is obvious that in this group of 35 positive records nervous instability, either primary or secondary, is the predominating factor. Heart disease was noteworthy by its absence.

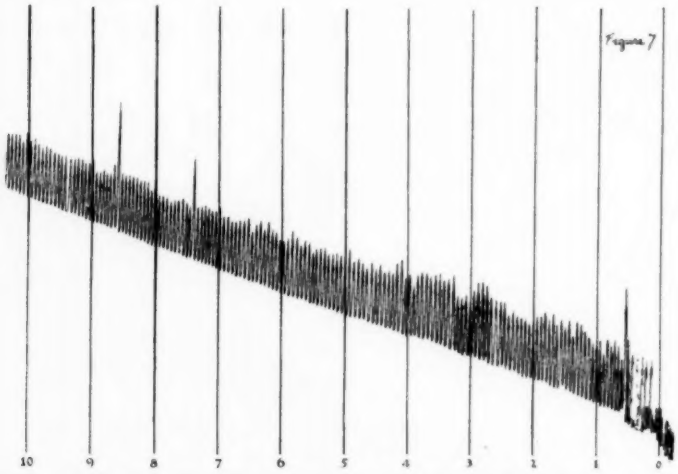

FIG. 7.—Respiratory tracing from patient (middle-aged woman) with a normal heart and without effort syndrome or nervousness. Three deeper breaths occurred in the interval of ten minutes. The respiratory rate was 16 (15 to 17).

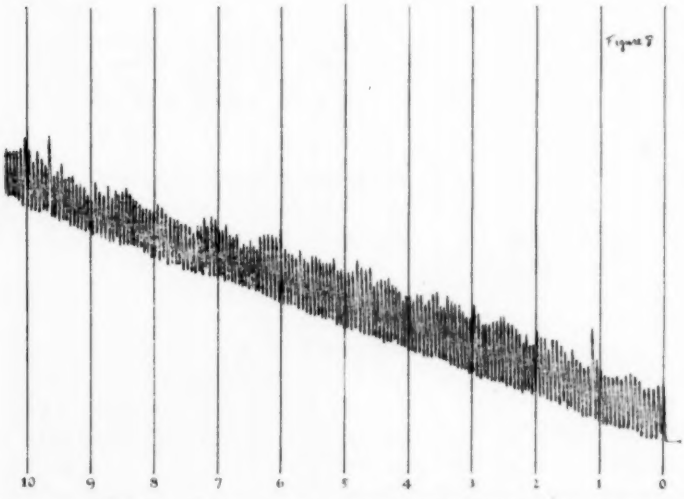

FIG. 8.—Respiratory tracing from a normal young woman (without effort syndrome or heart disease.) No sighs are noted although two breaths are slightly greater than the usual in the interval of ten minutes. The respiratory rate was 14 to 17 per minute.

To determine the frequency of excessive sighing in thyroid disease the spirograms of 10 cases of exophthalmic goiter and of 10 cases of myxedema were examined. Four of the hyperthyroid cases were positive (40 per cent) and 2 of the hypothyroid cases (20 per cent).

Finally, we studied the patients who sighed frequently to determine whether or not we could find any evidence of faulty action of kidneys, heart, lungs, or metabolism. None was apparent and we concluded that this symptom of sighing is solely a nervous phenomenon associated with fatigue or habit. In 2 cases with excessive sighing investigated there was no evidence of abnormal oxygen or carbon dioxid content in the blood.

Summary and Conclusions. 1. A study is here reported of the symptom of sighing, especially as it concerns cardiovascular diagnosis.

2. Statistical analysis showed that in four hundred normal control individuals sighing is a common finding, but of frequent occurrence in only 19 per cent. It was especially common as a frequent event in young women in the third decade of life (33 per cent), and it is generally recognized that it is this sex at this age that shows the greatest degree of nervous instability.

3. Further statistical analysis showed that frequent sighing is relatively rare in heart disease with or without congestive failure if there is no effort syndrome or marked nervousness (3 per cent of 100 cases).

4. In effort syndrome without heart disease excessive sighing is very frequent (80 per cent of 100 cases).

5. When effort syndrome or marked nervousness is combined with organic heart disease, excessive sighing is common (74 per cent of 50 cases). It is evident from the data previously cited that in these cases the sighing comes from the nervous state and not from heart disease.

6. Respiratory tracings from 5 cases of heart disease without congestive failure or nervousness showed an abnormal number of deep breaths in none; tracings from 8 cases of heart disease with congestive failure but without nervousness also showed an abnormal number of deep breaths in none; those from 8 cases of effort syndrome without heart disease showed an excessive number of deep breaths in 6 (75 per cent), those from 8 cases of combined effort syndrome or marked nervousness and heart disease showed increase of sighing respirations in 6 (75 per cent), and those from 12 cases without either effort syndrome or heart disease showed an abnormal number of deep breaths in none.

7. Of 200 routine unselected cases studied by respiratory tracings in the metabolism laboratory 25 showed abnormal sighing. Nervous instability was the commonest condition found in this group; no heart disease was present in any of the cases. Sighing was excessive

in 4 of 10 cases of hyperthyroidism and in 2 of 10 cases of hypothyroidism.

8. Frequent or constant sighing is a symptom of nervous origin, not dependent on disease of heart, lungs, kidneys, or thyroid gland. When it is present one should determine the degree of responsibility of the nervous system in the production of a state of ill health that may exist.

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BLOOD CHEMICAL STUDIES IN ARTERIAL HYPERTENSION.*

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The theory that arterial hypertension is due to the presence of some powerful constrictor substance in the blood was clearly formulated by Sir George Johnson in 1868. Johnson expressed the belief that the cause of arterial hypertension was the continued contraction of arterioles and observed that "the minute arteries in any part of the body may be excited to contract by their contents becoming abnormal and therefore more or less noxious to the tissues." Johnson saw in the observations of Gowers a confirmation of his theory that contraction of the arterioles is the cause of increased arterial tension. In 5 successive cases of Bright's disease in difference stages and with different degrees of tension, Gowers observed a direct relation between the contraction of the arterioles in the retina and the degree of arterial tension at the wrist. Gowers' observations were published in 1876.

Broadbent, in 1890, expressed his belief in the correctness of Johnson's views, stating that he considered hypertension to be due to an increased resistance in the capillaries, the cause of which "can scarcely be other than some substance present in the blood which acts directly upon the capillary walls." He adds that "the special material which plays this part is almost certainly nitrogenized waste which has not undergone the complete oxidation necessary for elimination."

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Von Monakow, fifty years after Johnson's publications, and thirty years after Broadbent's, expressed his belief that a "lasting increase in blood pressure is always due to abnormal contractions of arterioles" and that there is a "spastic component" present. Otfried Müller shares the views of von Monakow and describes constriction of the capillaries in both nephritis and "essential hypertension." More recently, Brown and Roth have studied the capillaries in arterial hypertension and while they find in the majority of cases no characteristic morphologic changes, yet the rate of flow is faster than normal and they note a rapid alternation of fast and slow suggesting intermittent closure of vessels. They state the impression "that there is definite capillary and arteriolar hypertonus with disturbances in the tonus control of the precapillary vessels."

The theories of Johnson and of Broadbent, together with the observations of Gowers, von Monakow, Müller, Brown and Roth, and others have been a constant stimulus to investigators to study the chemistry of the blood in hypertension. This had led to an intensive study of the well-known chemical constituents of the blood in hypertensives and has stimulated search for some unknown pressor substance in the blood.

The observations of Neubauer that certain patients with high blood pressure had a hyperglycemia, attracted much attention and led to an intensive study of the blood sugar in arterial hypertension. Hitzenberger and Richter-Quittner found the blood sugar regularly elevated in "vascular hypertension," with the highest blood sugar in the patients with the most marked hypertension. Kahler, however, after an investigation of this subject, states that in the vast majority of cases of long-standing hypertension, the fasting blood sugar is within normal limits. He found hyperglycemia especially in the complications of hypertension, in apoplexy, eclampsia and uremia. He states also that "Hochdruckstauung" is regularly accompanied by a hyperglycemia.

We have investigated this subject of hyperglycemia in 161 cases of arterial hypertension, 7 of whom were diabetics. In 154 cases, only 9 (5.8 per cent) showed fasting blood sugar above 110 mg. per 100 cc. and only 6 (3.7 per cent) showed fasting blood sugar above 120 mg. per 100 cc., the figures being 130, 135, 136, 139, 141 and 152 mg. per 100 cc. If we accept 120 mg. per 100 cc. as the upper limit of the normal fasting blood sugar, we find only 3.7 per cent showing a hyperglycemia, which is a rather unimpressive total.

While it is an unquestioned fact that hypertension unaccompanied by chronic nephritis frequently shows a hyperglycemia, our observations in hypertension unaccompanied by evidences of renal insufficiency, in agreement with those of Kahler, indicate that the great majority of hypertensives show a normal blood sugar.

Joslin has advanced the interesting idea that the hyperglycemia

found in hypertension is the response of the body to the heart's increased demand for sugar in order to maintain its excessive work. The presence of a large, overactive heart or a certain degree of cardiac failure in hypertensives showing a hyperglycemia makes the explanation more reasonable perhaps than the assumption of an increased adrenal activity.

Fishberg found that many patients with essential hypertension showed an increased uric acid in the blood. This observation has been repeatedly confirmed and was noted by Hitzenberger and Richter-Quittner and by Kraus. Fishberg studied 110 cases and found values higher than 3.5 mg. per 100 cc. in 44, or 39 per cent.

We have studied the blood uric acid in 170 cases of arterial hypertension, uncomplicated by frank nephritis. Of this number, 57 cases showed a blood uric acid above 5 mg. per 100 cc. and 113 cases above 4 mg. per 100 cc. If we accept 4 mg. per 100 cc. as the upper limit for normal, then 66 per cent of our series showed an increased blood uric acid. The highest value found was 10.5 mg., while 24 were 6 mg. or higher and 4 were 7 mg. or higher.

These observations indicate that while an increase in the blood uric acid is most striking in chronic nephritis, more than one-half of the cases of arterial hypertension who have no evidence of renal inadequacy show blood uric acid above the normal values.

Westphal has suggested that cholesterol may play a rôle in the production of high blood pressure and found a hypercholesterinemia in 71 per cent of 80 patients studied. Westphal believes that cholesterol increases the sensitiveness of the arterial musculature to adrenalin and in that way plays a rôle in hypertension. Hülse has been unable to confirm this work and thinks that while there may be a relationship between hypercholesterinemia and atherosclerosis, there is none between hypercholesterinemia and hypertension. Hülse noted that many patients with a hypercholesterinemia showed a marked atherosclerosis but no elevation in blood pressure.

Thomas has described an elevation in blood pressure produced by repeated injections of cholesterol into 4 rabbits. Thölldte, however, who repeated this work, obtained negative results and believes such results to represent only normal variations in pressure. Thölldte's conclusions seem quite warranted since the highest pressure recorded by Thomas was only 125 mm.

Kylin has been interested in the possible rôle of potassium and calcium in blood pressure. In hypertension, he has found a tendency for the blood potassium to be increased and the blood calcium to be lowered. This relationship of potassium to calcium, he has described as the K-Ca quotient. The quotient in health he finds to average 1.98, while in essential hypertension the average quotient is 2.33, and in bronchial asthma 2.48. The results obtained in bronchial asthma, together with other evidence, has led Kylin to the view that the autonomic nervous system plays an important rôle in the causation of essential hypertension.

The above observations showing that certain cases of arterial hypertension show increased amounts of blood sugar, blood uric acid and blood cholesterol, are of considerable interest, since they suggest possible metabolic disturbances in this disease. The difficulty in assigning a specific effect to them lies in the fact that neither glucose, uric acid nor cholesterol are pressor substances. It should be further recalled that diabetes, a disease in which the blood sugar is regularly increased, shows no elevation of blood pressure as a constant rule; that gout and leukemia, in which the blood uric acid is elevated, usually show normal blood-pressure values and that diseases in which the blood cholesterol is usually increased, such as cholelithiasis, lipoid nephrosis, atherosclerosis and diabetic acidosis do not show an increase in blood pressure as a constant or essential feature.

We have been studying for the past four years the possible rôle of the guanidin bases in the production of hypertension. It is well known that most of these bases, such as guanidin, methylguanidin and di-methylguanidin produce a marked rise of blood pressure when introduced into the body. It should be remembered, however, that certain guanidin derivatives, such as creatin and creatinin, have no specific effect upon blood pressure, while others, such as glycocyamin and glycocyamidin have a depressor effect. If the pressor guanidin compounds are present in the body in excessive amounts as the result of an increased production or a decreased excretion, they could produce a hypertension.

We have recently described a method by which small amounts of guanidin can be demonstrated in the blood. This method, which has been described elsewhere, is based upon the observations of Tiegs and Marston, that sodium nitroprusside produces in an alkaline solution an intense red color with guanidin compounds. We have applied this method to the study of the blood of persons with normal blood pressure, to that of patients suffering from chronic nephritis and to that of patients with so-called essential hypertension.

A study of 50 persons with normal blood pressure has shown us that the normal value for blood guanidin, if guanidin is present in the blood, does not exceed 0.2 mg. per 100 cc. and, as a rule, averages about 0.1 mg. per 100 cc.

The results obtained in 15 cases of chronic nephritis with hypertension are shown in Table I.

A summary of this table shows that all the cases of chronic nephritis with hypertension show a marked increase in "blood guanidin." This increase may, of course, be due to an oxidation in the body of creatinin into methylguanidin, although we have good evidence that it is not due to oxidation produced by the method employed. It is also important to remark that if the high blood values obtained in certain nephritics are actually due to guanidin, then guanidin is present in sufficient amounts to produce toxic symptoms such as convulsions.

TABLE I.—GUANIDIN READINGS IN A SERIES OF 15 PATIENTS WITH NEPHRITIS.*

No.	Age.	Blood pressure.	N.P.N.	Creatinin.	Creatinin.	Uric acid.	Guanidin readings.	Guanidin corrected.	Remarks.
1	51	194/130	86.0	3.6	5.1	..	0.65	0.39	
2	62	220/110	168.0	9.7	9.0	16.6	1.01	0.93	Uremia.
3	51	165/90	167.0	3.0	7.5	13.4	0.95	0.89	
4	51	180/120	67.0	3.8	..	7.0	0.37	0.27	
5	58	158/110	52.0	2.1	..	7.2	0.55	0.39	
6	60	180/90	39.0	1.4	..	..	0.46	0.43	
7	40	260/150	131.0	11.7	..	8.8	0.46	0.41	
8	48	170/110	60.0	2.5	2.6	..	0.52	0.29	Carcinoma of cervix.
9	64	240/145	74.0	2.7	6.0	4.7	0.49	0.37	
10	14	142/115	40.0	1.5	3.6	5.7	0.36	0.32	
11	42	140/88	83.0	6.5	..	..	0.75	0.69	Urea N. 75.
12	38	220/120	96.4	4.6	..	..	0.49	0.28	
13	40	180/130	315.0	12.0	5.6	5.3	1.1	0.67	
..	..	170/120	183.0	18.5	..	8.0	2.4	2.3	Uremia.
14	27	200/140	97.8	8.3	..	4.7	0.49	0.28	
..	..	200/140	89.0	11.0	1.4	3.9	0.67	0.54	
..	..	180/130	77.0	8.7	6.7	5.0	0.94	0.45	
15	24	160/110	188.0	13.7	2.3	..	1.6	1.3	Uremia.

* Blood chemistry in milligrams per 100 cc. of blood.

In Table II are shown the results obtained in 80 cases of hypertension belonging to the group of hypertension usually described as essential hypertension, in which there is no evidence of severe renal impairment and in which the blood nonprotein nitrogen and creatinin are within normal limits.

A summary of this table shows that 61 per cent of the patients have a "blood guanidin" higher than normal. These increases, while not very striking, are significant if the increased color is due to guanidin, since animals, when injected with methylguanidin, show a marked rise in blood pressure when the concentration of guanidin in the blood reaches the height which many of these patients show. Observations upon this phase of the subject have been reported elsewhere.

We wish to emphasize that we have no proof that this color reaction is produced by guanidin compounds. Such proof would only come with the isolation of guanidin from the blood, a very difficult procedure when the amounts are so minute.

It is also possible that this color reaction may be a delicate index of the renal function and that the increased amounts are due to a renal insufficiency not detectable by the usual tests of kidney function. But here again, if we are dealing with guanidin, these results should throw some light upon the etiology of arterial hypertension.

The 39 per cent of patients with hypertension, showing normal blood-guanidin values, is also an interesting group about which to speculate. Many of them were old people showing marked arteriosclerosis, who may have developed their hypertension during a

TABLE II.—GUANIDIN READINGS IN A SERIES OF 80 PATIENTS WITH ARTERIAL HYPERTENSION.*

No.	Age	Blood pressure.	N P N.	Creatinin.	Creatin.	Uric acid.	Guanidin readings.	Guanidin corrected	Remarks.
1	54	180/120	40 0	1 6	5 6	5 0	0 57	0 14	
2	50	156/110	35 7	1 3	4 9	3 1	0 44	0 27	
3	36	200/134	33 3	1 4	5 2	4 0	0 44	0 28	
4	74	176/110	30 0	1 3	4 6	3 3	0 22	0 13	Marked arteriosclerosis.
5	70	192/130	37 0	1 3	3 1	4 1	0 33	0 16	Marked arteriosclerosis.
6	40	176/110	37 5	2 0	4 5	5 4	0 36	0 09	Diabetes.
7	48	190/112	35 0	1 5	4 8	4 1	0 42	0 13	Carcinoma of breast.
8	72	175/110	29 0	1 4	3 8	2 4	0 23	0 04	Arteriosclerosis.
9	51	194/130	86 0	3 6	5 1	5 3	0 65	0 39	
10	45	210/100	33 0	1 2	3 0	2 7	0 38	0 2	
11	47	180/120	30 0	1 1	2 9	..	0 38	0 21	
12	63	196/98	31 0	1 3	2 7	3 2	0 33	0 12	Aortic insufficiency.
13	34	180/110	28 7	1 3	5 0	3 3	0 4	0 1	
14	44	185/120	28 0	1 2	3 8	3 6	0 48	0 25	
15	48	144/80	48 0	1 7	4 5	5 1	0 6	0 33	
16	57	190/130	39 6	1 4	4 5	3 46	0 34	0 07	
17	30	160/120	37 0	3 0	3 3	2 75	0 38	0 18	
18	57	178/124	37 5	2 4	3 0	3 2	0 43	0 25	
19	65	180/120	33 0	1 3	4 2	6 1	0 32	0 26	
20	55	178/95	35 0	1 3	3 7	4 7	0 32	0 25	
21	66	214/130	36 5	1 1	3 2	..	0 44	0 28	
22	66	214/130	36 5	1 1	3 2	..	0 44	0 28	
		220/134	33 0	1 3			0 42	0 3	
23	35	240/140	91 0	4 9	5 1	6 1	0 46	0 15	
			156 0	9 6	10 0	9 4	1 2	0 68	
24	42	190/120	92 0	4 3	3 5	..	0 46	0 25	
		170/110	31 0	1 2	6 2	..	0 56	0 3	
25	47	180/120	40 0	1 9			0 62	0 48	
26	68	234/130	33 0	1 2	5 6	4 1	0 55	0 29	
27	32	255/145	30 0	1 5	4 3	3 6	0 31	0 14	
28	54	180/120	34 0	1 2	4 6	6 0	0 31	0 19	
29	43	180/120	30 0	1 6	5 3	3 8	0 27	0 16	
30	42	170/110	31 0	1 5	5 1	4 9	0 36	0 17	
31	39	240/130	35 3	1 8	4 0	4 9	0 33	0 22	
32	65	200/130	71 0	2 6	3 5	..	0 33	0 2	
33	37	200/134	33 0	1 4	5 2	4 0	0 44	0 32	
34	70	192/130	37 0	1 3	4 4	4 1	0 33	0 17	
35	56	216/92	40 0	1 8	..	5 2	0 37	0 12	
36	72	200/120	48 0	1 3	5 0	3 2	0 41	0 19	
37	50	178/130	33 0	1 2	4 7	4 2	0 33	0 20	
38	43	180/110	30 0	1 6	5 3	3 8	0 27	0 16	
39	40	180/100	31 0	1 5	5 1	4 9	0 36	0 19	
40	39	230/150	35 0	1 8	4 0	4 9	0 33	0 22	
41	65	200/130	71 0	2 6	6 1	..	0 33	0 20	
42	61	228/120	31 6	1 2	6 0	3 4	0 35	0 17	
43	47	240/130	26 0	1 1	4 0	4 7	0 25	0 19	
44	64	180/130	35 0	1 1	3 5	4 1	0 23	0 17	
45	50	200/100	43 0	1 2	4 3	6 0	0 24	0 20	
46	65	275/140	35 0	1 1	2 7	3 6	0 25	0 21	
47	60	160/94	40 0	1 1	2 5	3 6	0 27	0 21	
48	50	180/85	34 0	1 1	4 5	3 3	0 47	0 33	
49	16	170/120	60 0	2 7	5 5	5 3	0 49	0 39	
50	56	175/105	20 5	1 2	4 1	2 8	0 44	0 31	
51	57	186/105	33 3	1 2	5 0	4 0	0 50	0 33	
52	55	190/100	37 0	1 2	..	3 1	0 44	0 30	
53	42	180/90	35 3	1 2	..	5 6	0 30	0 30	
54	44	200/120	16 5	1 1	2 7	4 6	0 35	0 27	
55	52	234/146	42 0	1 3	3 0	3 5	0 36	0 31	
56	56	180/110	18 5	1 2	4 0	5 0	0 36	0 34	
57	63	180/100	54 0	2 0	4 8	6 4	0 33	0 23	
58	76	210/80	46 0	1 2	..	..	0 37	0 29	
59	60	196/126	31 6	1 2	4 0	4 0	0 29	0 12	
60	50	200/120	79 0	1 2	..	..	0 26	0 23	
61	54	190/120	52 0	1 3	..	12 5	0 21	0 06	
62	40	200/120	35 0	1 8	..	6 5	0 44	0 34	
63	62	178/80	31 6	1 9	..	4 4	0 29	0 23	
64	52	180/110	27 0	1 2	..	3 8	0 38	0 24	
65	60	190/110	26 1	1 1	..	..	0 39	0 22	
66	44	180/110	30 0	1 2	..	..	0 37	0 21	
67	54	200/120	35 0	2 6	..	..	0 38	0 18	
68	61	216/120	35 3	1 2	..	..	0 39	0 26	
69	80	170/90	46 0	1 2	..	..	0 27	0 13	
70	65	180/110	52 0	2 0	..	4 5	0 44	0 31	
71	56	180/100	53 0	1 3	..	3 5	0 16	0 10	
72	74	170/100	32 0	1 4	..	3 3	0 22	0 12	
73	63	180/110	21 0	1 2	..	5 2	0 20	0 06	
74	66	180/110	38 9	1 3	..	5 6	0 23	0 20	
75	56	165/110	35 0	1 1	..	4 4	0 21	0 15	
76	54	180/120	50 0	1 4	..	3 8	0 62	0 44	
77	43	180/120	37 0	1 3	..	1 5	0 43	0 30	
78	72	160/110	20 0	1 5	..	2 5	0 54	0 40	
79	39	175/130	35 0	1 3	..	4 2	0 51	0 20	
80	40	170/110	30 0	1 4	..	..	0 28	0 23	

* Blood chemistry in milligrams per 100 cc. of blood.

period when they had high blood "guanidin" values and then continued with a physiologic or adaptation hypertension after the primary cause had disappeared. Others may be examples of a different type of hypertension having a totally different set of etiologic factors.

Conclusion. The only positive statement we wish to make is that certain hypertensives show in their blood an increased amount of some substance giving the same color response as guanidin and having certain chemical properties like those exhibited by the guanidin bases.

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A STUDY OF THE BLOOD PRESSURE OF PATIENTS WITH DIABETES MELLITUS.

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Before insulin was available most patients with diabetes died either of coma or of inanition. Insulin has made it possible for a new diabetic race to develop because with it such deaths can be avoided and, barring accident or incidental infection, the patients may live out their life expectancy. It is extremely important, therefore, to know whether or not diabetic patients are particularly likely to have hypertension.

Hypertension has been regarded by some authors as a significant complication of diabetes. Koopman said that in young patients blood pressure is normal, but in the older patients hypertension is the rule. Hitzenberger and Kylin found a large proportion of diabetic patients with hypertension. Katz-Klein found that the diabetes associated with hypertension is milder than the diabetes associated with normal blood pressure. Peterson found hypertension to be two and a half times as common in diabetic patients as in nondiabetic patients. Kramer recently studied 500 cases of diabetes, and concluded that hypertension in diabetics is "more common than we have been led to believe." One prominent American authority found an average systolic pressure of 139 mm. for diabetic patients of all ages; if this average had been "weighted" it would have been 148 mm. Rosenbloom, Elliott and others concluded that the blood pressure in uncomplicated diabetes is normal or slightly less than normal.

I have investigated the available material in The Mayo Clinic and have chosen 1001 diabetic patients for special study. Blood-pressure readings on these patients were obtained with a mercury manometer. The readings were made only after a period of rest in bed and were repeated by several observers.

Students of blood pressure have always deplored the lack of good controls. Most blood-pressure readings have been obtained from selected groups; the actual incidence of hypertension at various ages in the public at large has not been ascertained. Yet without this knowledge one cannot decide whether hypertension appears with greater frequency in any particular group of patients. Dr. W. G. Exton* has kindly supplied me with blood-pressure readings on a group of persons who applied for insurance. These data include not only readings of those accepted but of those rejected because of hypertension, and may be considered an estimate of the incidence

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of hypertension in the public at large, and this furnishes a control series which heretofore has not been available. The readings obtained in this group represent blood pressures of males and females ranging in age from fifteen to sixty years or more.

My cases were divided into two groups. In the first group all of of the 1001 were included. In the second, cases of nephritis, hyperthyroidism, and arteriosclerosis were excluded. The weeding out of cases of nephritis and hyperthyroidism was not difficult. I cannot say with certainty that all cases of arteriosclerosis were eliminated. However, those were excluded with obvious sclerosis of the peripheral or the retinal vessels or with suggestive cardiographic changes or angina pectoris.

Obesity is considered by some as a contributory cause of hypertension. A previous study of the diabetic patients in The Mayo Clinic showed that 90 per cent were overweight and that 80 per cent were more than 10 per cent overweight at some time before diabetes began; 54 per cent were still overweight after having had diabetes for varying lengths of time. The weight factor in the diabetic patients whose records were used for the present study was corrected by determining the number of patients who were thin (more than 5 per cent underweight), normal (+ or −5 per cent) and stout (5 per cent or more overweight). By correcting the averages of various age groups on this basis, the weight factor was properly considered.*

Arbitrary standards were chosen for high-pressure and low-pressure groups. A patient of any age was considered to have a high blood pressure if the systolic pressure was more than 150 mm. or if the diastolic pressure was more than 100 mm. A patient of any age was regarded as having a low blood pressure if the systolic pressure was less than 110 mm. or the diastolic was less than 70 mm.

Table I shows that 16.2 per cent of the male diabetic patients have a systolic blood pressure more than 150 mm., as against 2.4 per cent of Exton's normal males; 26.7 per cent of the female diabetic patients have a systolic pressure more than 150 mm., as against 4.3 per cent of Exton's normal females.

Table II shows that 15.6 per cent of male diabetic patients have systolic blood pressure lower than 110 mm., as against 2.5 per cent of Exton's normal men; 19 per cent of diabetic women have systolic blood pressures less than 110 mm., as against 8.1 per cent of Exton's normal women. These data, like those of the high blood pressure group, are averages for all ages.

The advocates of the theory that high blood-pressure predominates in diabetic patients can point to Table I to support their

* The weight factor was corrected against a "control" group, which was made up of patients registering in the Clinic. This was the best material obtainable with all the necessary details for a weight correction. The build distribution (thin, normal or stout) was satisfactory, and the blood pressure did not vary much from the insurance averages quoted. The correction was done in the diabetic cases, and weighed against the blood pressure averages of the same groups in the control cases.

TABLE I.—PERCENTAGE OF CASES IN WHICH THE SYSTOLIC PRESSURE WAS MORE THAN 150, OR THE DIASTOLIC PRESSURE MORE THAN 100.

Cases.	15 to 19 yrs.	20 to 24 yrs.	25 to 29 yrs.	30 to 34 yrs.	35 to 39 yrs.	40 to 44 yrs.	45 to 49 yrs.	50 to 54 yrs.	55 to 59 yrs.	60 + yrs.	Total.
					MALES.						
Systolic:											
Normal	0.6	1.6	0.4	0.9	1.0	1.8	4.4	6.3	9.4	21.0	2.4
Diabetic	...	...	4.5	...	...	25.0	6.0	30.4	32.5	22.0	16.2
Diastolic:											
Normal	...	0.2	0.7	0.5	1.4	1.6	3.5	4.9	7.9	13.2	1.7
Diabetic	...	...	...	...	...	16.6	4.0	4.3	15.2	8.0	6.1
					FEMALES.						
Systolic:											
Normal	0.5	...	0.4	1.3	5.2	5.8	14.5	12.3	25.0	33.3	4.3
Diabetic	16.6	...	...	10.5	21.0	12.1	32.0	35.0	39.0	43.0	26.7
Diastolic:											
Normal	...	...	0.4	1.8	3.5	2.9	7.7	1.5	12.5	20.0	2.3
Diabetic	...	...	...	...	5.2	3.0	8.5	15.8	19.5	13.9	9.4

TABLE II.—PERCENTAGE OF CASES IN WHICH THE SYSTOLIC PRESSURE WAS LESS THAN 110, OR THE DIASTOLIC PRESSURE LESS THAN 70.

Cases.	15 to 19 yrs.	20 to 24 yrs.	25 to 29 yrs.	30 to 34 yrs.	35 to 39 yrs.	40 to 44 yrs.	45 to 49 yrs.	50 to 54 yrs.	55 to 59 yrs.	60 + yrs.	Total.
					MALES.						
Systolic:											
Normal	7.6	3.4	2.8	2.1	2.3	2.1	2.2	0.7	...	...	2.5
Diabetic	18.2	23.1	24.0	31.5	39.2	12.5	14.3	16.7	15.6	5.7	15.6
Diastolic:											
Normal	26.0	17.1	15.2	10.9	7.1	8.3	6.6	4.1	4.7	5.2	10.9
Diabetic	44.0	46.2	32.0	36.8	36.0	21.4	14.3	16.8	15.2	2.9	20.0
					FEMALES.						
Systolic:											
Normal	15.3	13.1	10.5	7.1	4.0	1.4	1.6	1.5	3.1	3.3	8.1
Diabetic	...	17.6	27.6	27.3	...	12.5	4.4	4.0	5.3	3.4	19.0
Diastolic:											
Normal	25.4	24.7	22.0	15.1	8.6	7.1	5.1	6.1	3.1	3.3	16.3
Diabetic	44.0	29.5	20.2	22.8	4.3	22.5	2.9	12.1	10.5	4.2	23.7

opinion. On the other hand, the proponents of the view that low blood pressure might be the rule in diabetic patients may find encouragement in Table II. The final "weighted" averages of Table III (Charts 1 and 2) do not disclose any significant difference between the blood pressure of diabetic patients and that of normal persons. The apparent contradiction between results, tabulated in Tables I and II may be explained by the wide "scatter" of the blood-

TABLE III.—AVERAGE BLOOD PRESSURE IN NORMAL PERSONS AND IN DIABETIC PATIENTS WITH AND WITHOUT HYPERTENSION-PRODUCING COMPLICATIONS.

Age.	Normal persons (5727).		Diabetic patients without arteriosclerosis, nephritis or hyperthyroidism (652).		All diabetic patients (1001).	
	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
15 to 19	117.5±0.4	74.9±0.4	123.0±4.2	74.4±2.5	123.2±2.5	75.4±2.6
20 to 24	119.5±0.3	75.7±0.3	122.3±2.2	76.0±2.0	121.7±2.0	76.6±2.0
25 to 29	122.3±0.3	77.3±0.3	121.3±1.9	77.5±1.6	119.8±1.8	77.1±1.4
30 to 34	123.9±0.3	79.0±0.3	123.9±2.6	78.7±1.6	122.6±2.5	77.9±1.8
35 to 39	125.7±0.5	80.2±0.3	124.7±2.4	80.0±1.4	124.2±2.2	80.1±1.4
40 to 44	128.8±0.4	81.4±0.4	128.9±2.3	81.1±2.1	130.0±2.0	80.1±1.6
45 to 49	131.4±0.7	82.5±0.4	132.5±1.6	82.0±1.0	134.0±1.7	81.1±1.0
50 to 54	134.9±0.8	84.8±0.5	136.0±2.6	82.1±1.2	137.9±2.0	81.4±1.3
55 to 59	138.0±1.5	86.4±0.9	139.7±3.1	82.5±1.6	143.1±1.8	83.2±1.2
60+	141.3±2.0	87.4±1.4	141.1±2.1	82.6±1.2	144.0±1.4	84.1±1.8

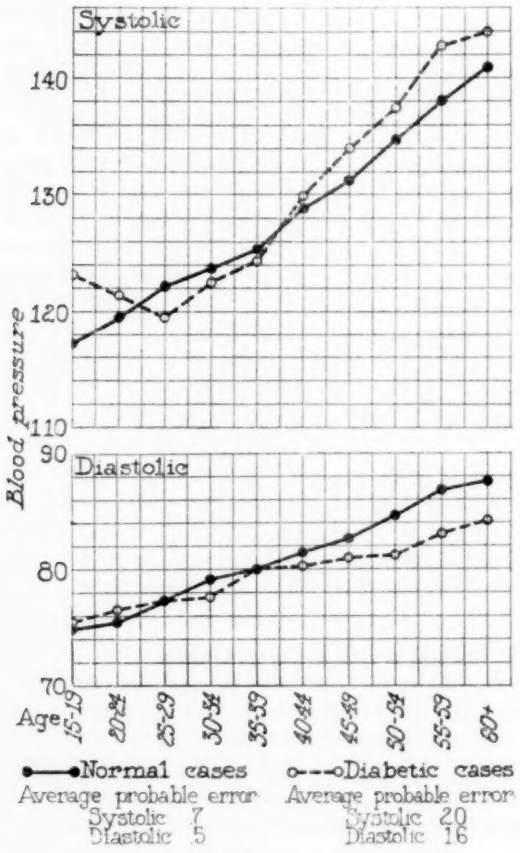

CHART 1.—The blood pressure of diabetic patients compared with the normal blood pressure.

pressure readings in diabetic patients as compared with the narrow scatter of blood-pressure readings of normal persons. The reason for the wide scatter is not clear; it may be due in part to an insufficient number of cases. There is, of course, a greater difference between the blood pressures of all diabetic patients and those of the normal group (Chart 1) than there is between the subgroups of patients who are free from nephritis, arteriosclerosis and hyperthyroidism, and the normal group (Chart 2).

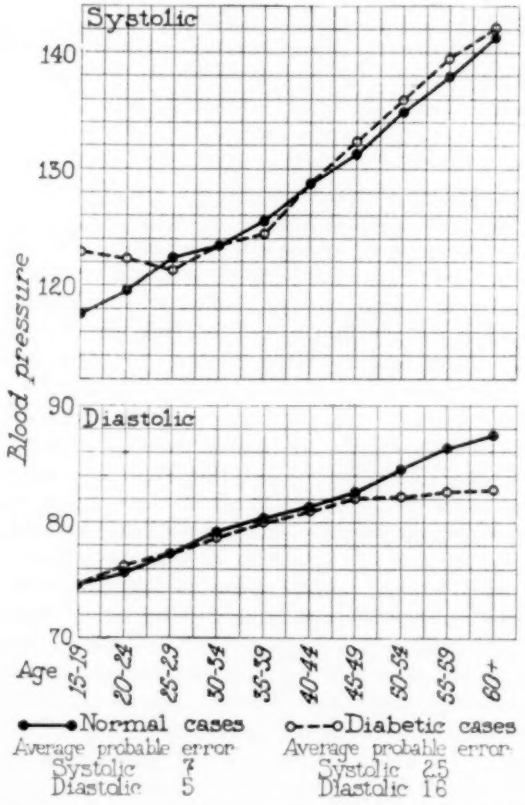

CHART 2.—The blood pressure of diabetic patients free from nephritis, arteriosclerosis and hyperthyroidism compared with normal blood pressures.

Uncontrolled diabetes particularly in the severer forms enforces a reduction of weight. Although adequate amounts of food are eaten, the food is not all metabolized and the result is the same as if a nondiabetic person ate a submaintenance diet. Weight reduction is an important measure in treating diabetes. Weight loss, therefore, is an important factor in cases of treated and untreated diabetes alike. Benedict, in his study of the effects of restricted

diets on a group of young men, found among many other significant facts a definite lowering of the systolic and diastolic blood pressure. The blood pressure of Benedict's fasting man became lower as the fast continued.

From the foregoing one is led to believe that the blood pressure of diabetic patients might be higher if the element of weight loss did not enter into consideration. In this study the results tabulated in Table I might, therefore, approach the truth much more closely than the results shown in Table II. If the figures in Table II can be discounted it would mean that diabetic patients as a class were more susceptible to hypertension than normal persons. On the other hand, several points with reference to these cases should be considered: (1) Prolonged undernutrition in treated and untreated cases would be more common in the younger patients. The younger patients form but a small part of the whole group. (2) In many instances the patients did not lose much or any weight until treatment was started and the blood-pressure readings used in this study were those obtained soon after admission to the hospital. (3) Corrections for weight were made against a group of routine patients coming to the Clinic, and this group included patients who had lost weight, as well as those who had gained.

Summary. Heretofore students of this problem have usually considered only half of the picture, that is, they have considered only the high pressures. In this way one finds that there are more diabetic patients than there are normal persons with systolic pressure of more than 150, and from this fact alone one might conclude that diabetic patients are more likely to have hypertension than normal persons of comparable age groups (Table I). On the other hand, a similar analysis of those with low pressures shows that more diabetic patients have a systolic pressure less than 110 than normal persons of comparable age groups. One might conclude from Table II that hypotension is more common in diabetic patients than in so-called normal persons. If, however, the high and low pressures of diabetic patients, and of normal persons are averaged, a significant difference is not found (Table III and Chart 2).

Conclusions. An analysis of the blood pressure of the diabetic patients seen in The Mayo Clinic does not provide clear evidence to show that diabetes of itself promotes hypertension. If the blood pressure of diabetic patients is elevated it suggests the presence of some associated abnormality which of itself is responsible for the hypertension.

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AN EXPERIMENTAL STUDY OF THE INFLUENCE OF FERROMAGNETIC CUBIC AND PARAMAGNETIC AMORPHOUS IRON OXID ON THE BLOOD.

(In Simple Anemia and in the Normal.)

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It is now recognized that there is a normal iron reserve in the tissues of the healthy body available for the building up of hemoglobin. The need for iron in some types of clinical anemia may be explained, in part at least, by the depletion of this reserve. The fundamental studies of Whipple[1] and his associates in experimentally controlled anemias have laid the foundation for an ultimate understanding of the many factors involved. In the simple anemia following brief periods of hemorrhage Hooper, Robscheit and Whipple found that medicinal iron did not hasten or increase the regeneration of hemoglobin. This observation has been repeatedly confirmed by many others[2,3] using the oral, subcutaneous and intravenous routes for administration of various iron salts. However, Whipple and Robscheit-Robbins did find in their dogs that, in the presence of a long continued, severe anemia due to repeated hemorrhages, iron in the form of Blaud's pills had beneficial effects, though never so striking as those obtained with the feeding of liver. Riecker[4] has recently emphasized the depletion of available iron after prolonged hemorrhage, particularly as it is related to the synthesis

of hemoglobin in distinction to cell regeneration, and urges the efficacy of iron therapy (ferric citrate and ferrous carbonate) in the treatment of this type of anemia. In as much as iron may be inactive in some anemias and quite potent in others the mechanism of this reaction is not simple, and it may very well include factors other than that involving a mere attempt at replacement of iron necessary for the hemoglobin molecule.[5]

Utilizing the nutritional anemia in rats, Mitchell and Vaughn[6] have made an extensive comparative study of the relative availability of different forms of iron, as evidenced by the hemoglobin response. They found that the addition to the diet of small amounts of ferric citrate, ferric albuminate, ferric chlorid, and ferric acetate apparently produced good results; peptonized ferric oxid, saccharated ferric oxid, saccharated ferrous carbonate and ferrous iodid gave only fair improvement; while ferric oxid, ferrous carbonate, ferric potassium tartrate, ferrous lactate, ferrum reductum and ferrous sulphate all yielded poor results. They emphasize the relationship of solubility of the iron salt to its efficacy and the advantage in general of the ferric over the ferrous forms. Hart and his coworkers[7] found that in the nutritional anemia induced in rabbits by an exclusive diet of whole milk, inorganic iron in the form of Fe_2O_3 was ineffective; but when in addition to the iron oxid, fresh cabbage, or an alcoholic extract of dried cabbage, or the ash of cabbage or lettuce was used, the anemia was prevented. They also found that the anemia following the whole milk diet could be prevented by another form of iron, namely, impure soluble $FeSO_4.7H_2O$. The question of the relative merits of ferrum reductum, ferric and ferrous iron seems still to be a debatable one.

With the discovery of a ferromagnetic cubic form of iron oxid by Welo and Baudisch,[8] followed recently by the advocacy of its use therapeutically under the trade name of "siderac" in the German literature, it has seemed desirable to analyze its effect under the controlled conditions of a simple anemia. Through the generous coöperation of Dr. Baudisch we have had at our disposal chemically pure ferromagnetic iron oxid (Fe_2O_3) and the paramagnetic amorphous iron oxid ($Fe_2O_3.xH_2O$) prepared by him. This new amorphous iron oxide ($Fe_2O_3.xH_2O$) is different from the rhombohedral, inactive iron oxid (Fe_2O_3), which was prepared from its cubic ferromagnetic form.* These substances were put up in gelatin capsules, each containing 3 mg. of the ferric oxid triturated with sugar of milk 1 to 10. Rabbits were employed for the experiments. The iron was administered by mouth in doses of either 3 or 6 mg. per day, in rabbits ranging from 1800 to 2800 grams in weight. This is on the basis of a dosage of 100 to 200 mg. for the adult human.

* The amorphous paramagnetic iron oxid has been prepared in an entirely new way. The method of preparation will be given in another journal.

Ferromagnetic Iron Oxid. Rabbit R429 (Chart I) was bled four times from the heart at forty-eight-hour intervals, which reduced the red cells from 6,100,000 to 3,250,000 (February 21, 1928) and the hemoglobin from 67 per cent (Newcomer) (11.33 gm. per 100 cc. blood) to 42 per cent (February 23, 1928) (7.10 gm.). On the sixth day after the last bleeding, the total count of the red cells had returned to 5,310,000, hemoglobin 60 per cent (10.15 gm.), and on the sixteenth day the count reached 6,500,000, hemoglobin 65 per cent (10.99 gm.). The original color index was 0.54; at the time of greatest anemia it was 0.73; on reaching 5,310,000 cells, it was 0.56; with 6,500,000 cells, 0.50; and twenty-two days after the original bleedings, when the red blood cells were 5,380,000 per c.mm., the hemoglobin (color index 0.62) had returned to its original level of 67 per cent (11.33 gm.).

The same rabbit was again bled from the heart on successive days, until the red cells were only 3,070,000 and the hemoglobin 36 per cent (6.09 gm.), color index 0.58. At this time the administration of ferromagnetic iron oxid, 6 mg. per day by mouth, was started. Again the 5,000,000 point was regained on the sixth day with the hemoglobin 54 per cent (9.13 gm.) and color index 0.54; but this level was not maintained. The majority of

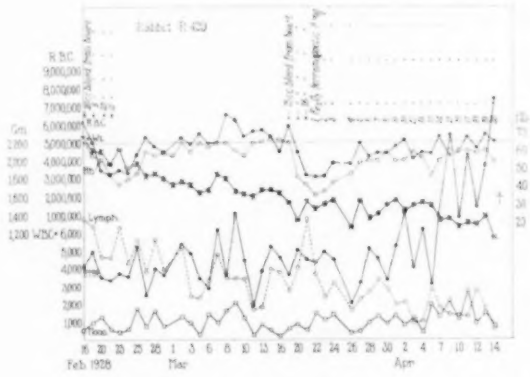

CHART I.—Studies of the blood of Rabbit R429.

the counts thereafter remained between 4,000,000 and 5,000,000, with the hemoglobin fluctuating between 47 per cent (7.95 gm.) and 60 per cent (10.15 gm.), and color index between 0.53 and 0.64, with a final in dex of 0.54. The differential count of the white cells was not remarkable, except for the terminal rise in neutrophilic leukocytes. There was a gradual loss in weight from 2200 gm. to 1125 gm. during the period of observatio n. This animal died on the twenty-third day after the iron was started. Aside from some small patches of bronchopneumonia in the right upper lobe of the lungs, accounting for the leukocytosis, there was no obvious cause of death at autopsy. The spleen weighed only 0.4 gm., a decrease proportional to that of the body weight, and it showed no hemopoiesis. The bone marrow of humerus and femur was very elastic, gelatinoid, granular, mottled, and grayish-brown in color. The distal end of the tibia, usually acellular and fatty, showed no hemopoiesis. Histologically, the red cells seemed distinctly decreased in relative and absolute numbers. The majority of the red cells were late erythroblasts with only a few younger cells and normoblasts. Sabin and Doan[9] have found the normoblasts to constitute 69 per cent of the nucleated red cells in the marrow of normal rabbits. There was also a definite shift to the left in the myeloid series, myelocytes "C" being

markedly outnumbered by the "B" myelocytes, whereas the normal percentage of myelocytes "C" is 85 per cent.[9]

Under the administration of ferromagnetic iron oxid, then, this rabbit, during equivalent periods of observation after a simple anemia, averaged a return in the red cells to a level approximately a million less than that attained on a normal diet without iron, and the hemoglobin averaged 0.85 gm. to 1.7 gm less. If the normal iron reserve was depleted during the first period of regeneration of red cells, then the iron subsequently given was unable to replace this store. For, though the total cells had returned at the end of three weeks in each case to approximately the same level, the hemoglobin was 7 to 10 per cent less on the second recovery, making the difference in color indices 0.62 and 0.54 respectively.

To test whether an iron depletion during the first recovery from bleeding (Chart I) had to do with the slower recovery with the iron after the second bleeding, Rabbit R423 was bled from the heart on six occasions at forty-eight hour intervals, which reduced the red cells from between 5,000,000 and 6,000,000 to 3,000,000. The hemoglobin dropped from about 70 per cent (11.84 gm.) to 39 per cent (6.59 gm.), and the color index changed from 0.59 to 0.62. The daily administration of 3 mg. of ferromagnetic iron oxide by mouth was started at once. In 3 control rabbits rendered anemic and permitted to regenerate cells under the conditions of a normal, adequate, herbivorous diet, the original level of red cells was regained on the sixth, eighth and tenth days, and the hemoglobin on the tenth, eighth and tenth days respectively. In Rabbit R423, on the other hand, the original level of red cells was not reached until the sixteenth day, and that of the hemoglobin not until the twentieth day. The differential count of the white cells was not unusual and there was a well-maintained weight curve. The color index at the end of twenty-two days was 0.65.

Now the iron was discontinued for nine days and a second series of four cardio-punctures, at twenty-four-hour intervals, was carried out, reducing the total red cells to 2,700,000 and the hemoglobin to 33 per cent (5.58 gm.). This time 6 mg. of ferromagnetic iron oxid were given as the daily dose. Again there was a strikingly prolonged period of recovery, the total red cells first reaching the 5,000,000 mark on the sixteenth day of treatment, but with the average count remaining well under this level until after the iron was stopped at the end of twenty-one days. The hemoglobin, too, remained under 60 per cent (10 gm.) for this entire period. There was some loss of weight during the second period of observation.

Ferromagnetic iron oxid, under the conditions of the experiment, did not merely fail to aid in the regeneration of hemoglobin after simple anemia, but seemed actually to delay the return to the normal. In view of this latter finding, tests were carried out of its effect on the blood condition in normal rabbits.

Rabbit R304 (Chart II) was followed over a period of six months with complete blood studies at weekly intervals. During this control period the red cells remained above 6,000,000 for the most part, the cells and hemoglobin reaching 7,000,000 and 85 per cent (14.38 gm.) respectively just prior to the initiation of the iron therapy. There had been a gradual increase in weight during the six months, from 2000 gm. to 2700 gm. Ferromagnetic iron oxid, in daily doses of 6 mg. by mouth, was begun. During the succeeding two months in which it was regularly given, there was a gradual but steady decline in the red cells to a low point of 4,380,000, accompanied by a fall in the hemoglobin to 63 per cent (10.65 gm.)—an

average decrease of 1,500,000 to 2,000,000 cells and an average fall of more than 15 per cent (2.5 gm.) of hemoglobin (maximum fall 22 per cent—3.72 gm.). Instead of a steadily rising weight curve there was, after the iron was started, a decrease in weight. The white blood cells maintained their usual relative proportions.

Fifty-seven days after the iron was begun, this animal was killed by air embolism and autopsied. There was nothing unusual in the tissues or organs in the gross, except in the bone marrow. On surveying the marrow of the several long bones, it was clear that there was quantitatively less active hemopoietic tissue in them than is found in the normal rabbit. The femoral marrow on both sides was mottled with foci of fat, there being one area of about 1 cm. in extent, just proximal to the middle of the diaphysis, entirely fatty, whereas under normal conditions it is usual to find this cavity filled with red marrow. Both humeri showed areas of fat near the distal ends of the bones; the distal ends of both tibiæ and the entire extent of both radii and both ulnæ were yellow fat, and this in the presence of a falling red-cell count. The gross appearances were confirmed histologically.

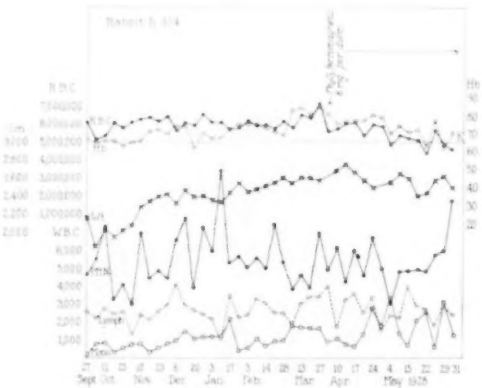

CHART II.—Studies of the blood of Rabbit R304.

The fat was extremely unevenly distributed in the marrow, some areas showing nothing but enormously distended fat cells, in contrast with other areas, where the fat was in a finely divided state. There was a marked increase in the clasmatocytes, all being filled with phagocytized, yellowish-brown pigment, such as is encountered under circumstances of abnormal blood destruction. A differential count of representative preparations, from which 2000 cells were counted, resulted as follows: Myeloid cells 48 per cent, erythroid cells 48.2 per cent, clasmatocytes 1 per cent, primitive cells 2 per cent, lymphocytes 0.25 per cent, monocytes 0.05 per cent. The myeloid-erythroid ratio was thus 48 to 48.2, whereas for the bone marrow of normal rabbits it is 70 to 25.[9] Of the nucleated red cells, 51 per cent were normoblasts, 35 per cent late erythroblasts, 13 per cent early erythroblasts, and 0.04 per cent megaloblasts. This is in contrast to the average of 5 normal rabbits, as given by Sabin and Doan:[9] Normoblasts 69 per cent, late erythroblasts 26 per cent, early erythroblasts 4 per cent, and megaloblasts 0.04 per cent.

It is evident that the total extent of blood-forming tissue was so reduced in Rabbit R304, and the percentage of available normoblasts so decreased,

as contrasted with other stages of nucleated red cells, that the relative increase in erythroid to myeloid tissue was insufficient to maintain the original level of red cells in the peripheral blood. The spleen showed no compensatory hemopoiesis.

The experiments appear to show that the administration of ferromagnetic iron oxid not only fails to aid in the regeneration of blood during a simple anemia but actually causes anemia in normal animals. In four experiments with this form of iron the results have been consistent.

Amorphous Iron Oxid. Three experiments with controls to correspond were carried out with the amorphous iron oxid. In Rabbit R422 (Chart III)

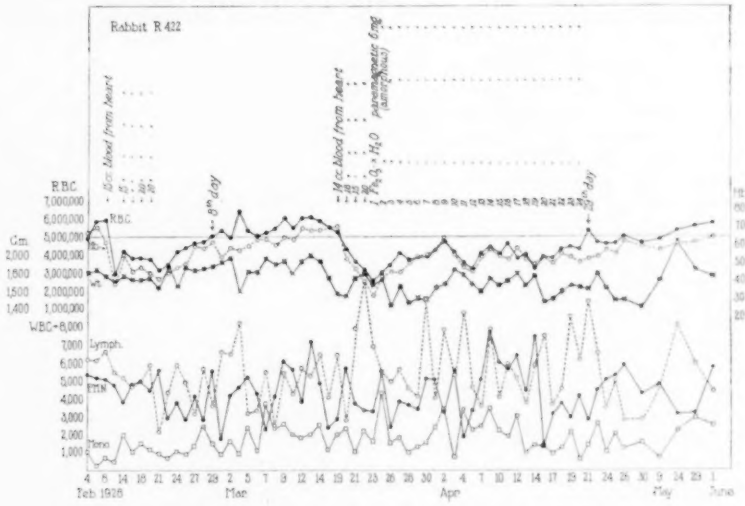

CHART III.—Studies of the blood of Rabbit R422.

the red blood cells were reduced from between 5,000,000 and 6,000,000 to 3,200,000 by a series of five cardiopunctures, the hemoglobin falling from between 60 per cent and 70 per cent (10 and 12 gm.) to 42 per cent (7.10 gm.). By the eighth day, the red cells had returned to 5,000,000 with hemoglobin 62 per cent (10.49 gm.) and color index 0.62 (original color index 0.67). The red cells and hemoglobin continued to maintain their normal range of fluctuation as originally determined until a second series of bleedings from the heart again reduced the red cells to 2,600,000 and the hemoglobin to 33 per cent (5.58 gm.), color index 0.63. At this point a daily dosage of 6 mgm. of amorphous iron oxid, paramagnetic, by mouth, was begun. During a period of time similar to that of the first observations, twenty-eight days, the red cells never returned to 5,000,000, averaging between 3,000,000 and 4,500,000 for the most part. The percentage of hemoglobin paralleled closely the total count, ranging from 46 per cent (7.78 gm.) to below 60 per cent (10 gm.), except for one reading of 65 per cent (10.99 gm.). Following the stopping of the iron by mouth, both red

cells and hemoglobin showed a tendency to increase to the original level of above 5,000,000 and 10 gm. hemoglobin. Whereas after the first bleedings the total red cells had returned to 5,000,000 on the eighth day after the last hemorrhage, after the second series they did not reach this until the twenty-ninth day, and then only after the cessation of the iron. The hemoglobin per red cell was slightly more than in the original period of observation, the color indices ranging from 0.71 to 0.65, so that the depressant effect was primarily one on the replacement of cells. There was a decided increase in body weight after the iron was discontinued. The white cells showed a consistent lymphocytic predominance, as happens in certain rabbits, with an occasional rise in monocytes, but otherwise nothing remarkable.

A similar experiment, but with the order reversed, was carried out in Rabbit R430 (Chart IV) to control the preliminary depletion of iron as a

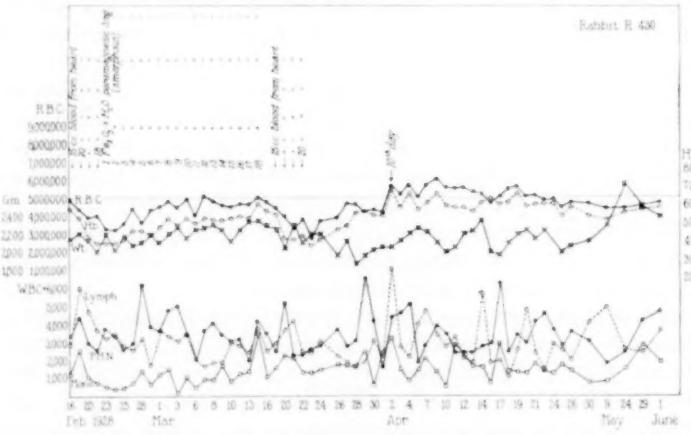

CHART IV.—Studies of the blood of Rabbit R430.

possible explanation of the second delay in regeneration of red cells. After reducing the red cells by repeated cardiopunctures to 3,200,000 and the hemoglobin to 40 per cent (6.76 gm.), 3 mg. of amorphous iron oxid were given daily. The red cells first passed the 5,000,000 mark on the thirteenth day thereafter, and the color index reached 0.52, though it was not maintained at this level. The hemoglobin did not rise to 55 per cent (9.3 gm.) until the nineteenth day. The iron was stopped after twenty-two days (18 doses), when the color index was 0.60, and after an interim of five days the red cells were again reduced through repeated bleeding from the heart. From a low point of 2,800,000 red cells, with hemoglobin of 39 per cent (6.59 gm.) and color index 0.69—a lower absolute level than that obtained in the previous observation—the count rose to 5,700,000 by the tenth day, hemoglobin 70 per cent (11.84 gm.), color index 0.61, with the level maintained.

In this instance it seems clear that the administration of 3 mg. daily of the amorphous iron oxid retarded the return to normal in both red cells and hemoglobin and prevented the overcompensation seen on chart IV after the second bleeding.

Rabbit R112 was followed by means of complete blood studies at weekly intervals from October, 1926, to April, 1928. The red cells throughout this period remained above 6,000,000, with the exception of a very occasional count of between 5,500,000 and 6,000,000. The hemoglobin ranged between 75 per cent (12.69 gm.) and 90 per cent (15.22 gm.), reaching a high point of 97 per cent (16.41 gm.) on April 3, at which time 6 mg. of amorphous iron oxid daily by mouth were started. During the following two months both red cells and hemoglobin showed a decline to low points of 4,900,000 and 69 per cent (11.67 gm.) respectively, a fall of between 1,000,000 and 1,500,000 in cells and of 28 per cent (4.74 gm.) as a maximum for the hemoglobin.

Here again in the normal rabbit the initiation of iron oxid therapy by mouth produced a definitely depressant effect.

Summary. In general, these observations tend to indicate that both the ferromagnetic iron oxid (Fe_2O_3) and paramagnetic iron oxid ($Fe_2O_3.xH_2O$) act similarly in their effect on hemopoiesis in the rabbit both in the normal state and in that of a simple anemia after hemorrhage. The magnetic property apparently exerts no significant biological effect.* The emphasis has been placed heretofore upon the presence or absence of a beneficial effect in considering the various iron salts in blood deficiencies. The studies here reported direct attention toward the possibility of a positively unfavorable effect, a definite depression of hemopoiesis, attending the administration of iron in certain forms.

From this brief report of the effect of ferromagnetic and paramagnetic iron oxid in the normal rabbit and in rabbits suffering from a simple anemia after hemorrhage, it is suggested that this treatment in clinical cases of secondary anemia may be a disadvantage and should not be undertaken without further experimental data.

* An observation which may be significant in this connection was made by Welo and Baudisch;[8] they found that ferromagnetism and catalytic activity in iron oxid have no essential relationship.

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THE TREATMENT OF SPRUE WITH LIVER EXTRACT (343).

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AND

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In a previous note[1] we reported the results of treatment of a patient with sprue by the high-liver diet of Minot and Murphy. The rationale of the procedure was based on the similarity of sprue and pernicious anemia. The case, in brief, concerned itself with a man, aged forty-three years, seen in the summer of 1927, who had gone to the Philippines in 1924 and returned to this country in 1926. For fourteen months there had been continuous diarrhea with huge, pale, frothy stools, attacks of stomatitis and general debility. There was moderate anemia with high color index, leukopenia, anisocytosis and poikilocytosis and many large cells. Within a a week after starting the liver diet the bowels were almost normal and there was a rise in reticulocytes to 6 per cent followed by improvement in the red-cell count. Within two months the patient left the hospital feeling perfectly well, having gained 25 pounds. The bowels were practically normal and the blood count showed over 5,000,000 red cells with 100 per cent hemoglobin.

The present report deals with 2 further cases of sprue in which satisfactory remissions were obtained by the use of Liver Extract 343 (Lilly).

Dietetic Treatment of Sprue. All the accounts of sprue abound in dietary suggestions: the milk cure, the strawberry cure, the banana cure and the water-meat cure may be mentioned as examples. The details of regimen vary with the experience of different observers. It is quite clear, however, that none of these methods of treatment have possessed any reliable degree of effectiveness, and many of the good results may be explained by "spontaneous" remissions which are common in sprue as well as in pernicious anemia. While liver is mentioned occasionally as being beneficial (especially in the form of liver soup) we can find no accounts of adequate liver feeding in sprue in the sense in which it has been carried out in pernicious anemia. Occasional statements that liver is actually harmful may also be found.[2]

Relation of Sprue to Pernicious Anemia. As we said above, the intensive use of liver in the present series of cases was suggested by the similarity of sprue and pernicious anemia. The question of the relationship of the two diseases and their possible identity has been thoroughly discussed in the recent literature,[3] but the matter

does not seem to be finally settled. Ashford's studies on Monilia seemed for a time to favor a specific etiology in sprue; but Nye[4] has recently found yeasts in both sprue and pernicious anemia and brings forward good evidence that they are secondary invaders in both conditions. Central-nervous-system changes are said to be less common in sprue than in pernicious anemia and the typical "sprue stool" is certainly not often seen in the latter; however, these are not absolute distinctions. We have been impressed by the undoubted presence of considerable amounts of free hydrochloric acid in the gastric secretions of the cases herewith reported. If, as most observers feel, anacidity is an essential feature of pernicious anemia, one would seem to be dealing with a different condition. At any rate, until the specific cause of both diseases is discovered they may well be regarded as distinct clinical entities.

Case Reports. CASE I.—J. S., aged twenty-five years, an American mechanic, entered the hospital on February 29, 1928, complaining of pain in the stomach, diarrhea, weakness and bloody urine.

The past history seemed unimportant except for the fact that he had been in the Philippines from 1924 to 1927 in the army. His previous health had been good.

In 1925, and again in 1926, he had brief attacks of diarrhea, featured by gaseous distention of the abdomen and passage of huge pale, frothy stools. There were cramps and tenesmus. In December, 1926, the diarrhea recurred and persisted up to the time of entry. The patient stated that there had been five or six movements daily and he estimated the usual size of the passage as "about a gallon." There had also been frequent attacks of "sore burning mouth." At about the time of onset of the diarrhea he began to pass bloody urine. This was very marked at times and was still present on entry. There had been great loss of weight.

On examination he seemed extremely ill, prostrated and very pale. There was marked papillary atrophy of the tongue which appeared red and raw. There was a systolic murmur at the apex and the pulse rate was 120. The abdomen was distended and tympanitic. The liver and spleen were not felt. No definite neurologic changes were discovered. The blood count was: red blood cells, 740,000; hemoglobin, 25 per cent (Sahli); leukocytes 2500; polymorphonuclears, 39 per cent; lymphocytes, 56 per cent. There was marked anisocytosis and poikilocytosis and moderate diffuse basophilia. The urine was brownish-red and contained innumerable red blood cells. There was much albumin, but no casts were seen. The stools were pale yellow, foul and extremely bulky. They contained a large amount of fat; there was no blood, pus, mucus or parasites, but there were many yeasts. Gastric analysis after histamin showed a maximum ten-minute secretory volume of 26 cc. with free HCl 105 and total acid 111. Scrapings from the tongue yielded monilia.

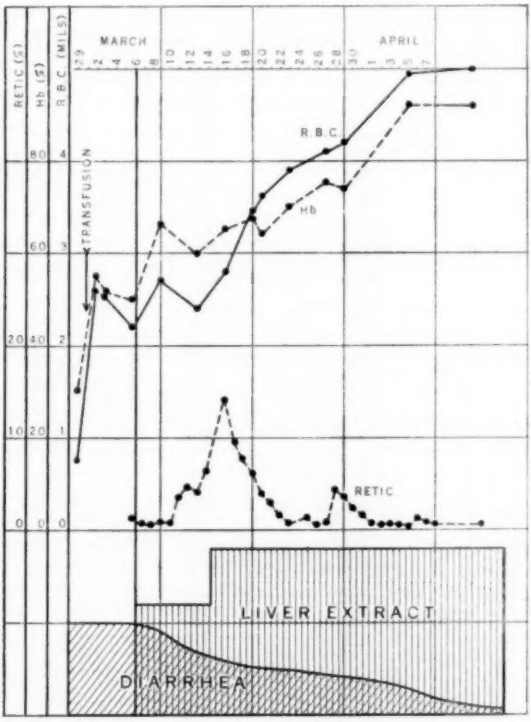
An investigation of the urinary tract by Dr. Dillon showed a urethral stricture and injection and varicosities of the bladder wall, which were evidently the source of the bleeding. On March 1, a suprapubic cystotomy was done and a periurethral abscess was incised. After suprapubic drainage was established the urine gradually cleared up. The wound was closed later and when the patient left the hospital the urinary tract was in normal condition.

On March 1, a transfusion of 600 cc. of citrated blood was given as a preliminary to the operation. That this played no apparent part in the sub-

sequent course is suggested by the fact that the blood count was falling when liver extract was first given. The effects of the liver therapy are shown in Chart I. Aside from the extract, equivalent to 400 to 600 gm. daily, treatment consisted of bedrest, liberal diet without liver and symptomatic measures.

The response to liver was clean cut in spite of the fact that at first there was still considerable loss of blood in the urine. On the fourth day of treatment he began to feel better, it was less difficult to eat, the stools became less bulky and the abdominal cramps and sore mouth improved. Progress

CHART I.



was uninterrupted and the patient left the hospital thirty-seven days after the liver treatment was begun. The red cells had reached 5,000,000; there had been a gain of about 30 pounds in weight. There were one or two soft or formed brownish stools daily which still contained, however, an excess of fat. He felt perfectly well.

In summary, then, a patient with sprue with marked diarrhea, stomatitis, emaciation and anemia, complicated by urethral stricture and hematuria, responded remarkably to liver extract and within five weeks was symptomatically well.

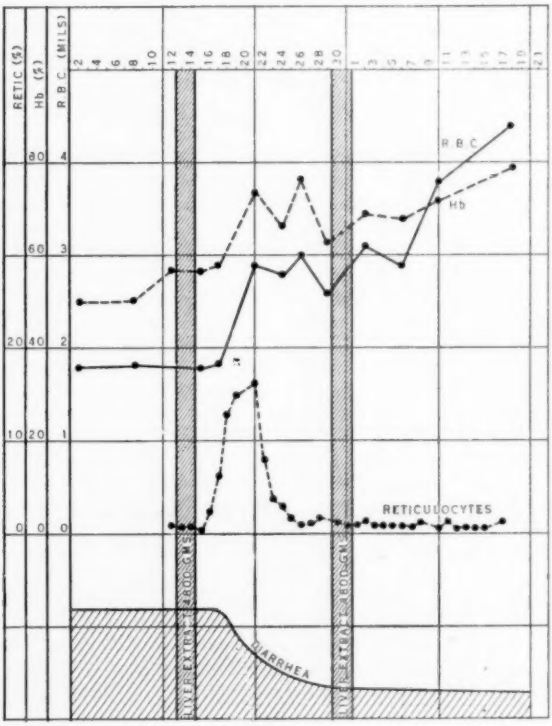
CASE II.—J. G., a Spanish laborer, aged fifty-seven years, entered the hospital February 27, 1928, complaining of nausea, gas on stomach and diarrhea of three years' duration.

The past history seemed unimportant except for the fact that for ten years there had been some gas and discomfort after heavy meals.

Three years ago he began to have three to five loose bowel movements daily associated with moderate abdominal discomfort. He had lost 26 pounds and has felt generally run down. His habits are not remarkable and he has been in the United States for the past twenty years.

On entry he looked sick and worn. There was moderate undernutrition (weight 52 kg.) and marked pallor without distinct yellowish tint. The tongue showed papillary atrophy with redness of the margins but no ulcerations. The liver and spleen were not felt. No neurologic changes were made out. The remainder of the physical examination showed nothing abnormal.

CHART II.



The blood count on entry was: red blood cells, 2,000,000; hemoglobin, 50 per cent; leukocytes, 4000; polymorphonuclears, 50 per cent; lymphocytes, 40 per cent. There was marked anisocytosis and poikilocytosis and many macrocytes were present. The stools were moderately bulky, light yellow, soft and pasty, with much fat. Monilia were present, but no parasites. The stools at first numbered two to five per day. Gastric analysis showed free HCl, 23; total acid, 34. After histamin, the ten-minute secretory volume was 17 cc. The free HCl reached 60, and the total acid 70.

It was evident that the patient fell into the general group of sprue or pernicious anemia. In view of the character of the stools and the presence of free HCl, the former seemed the most logical diagnosis. It was decided to try the effects of large doses of liver extract, given over a brief period of time. The patient was kept in bed on a liberal general diet without liver and on March 13 and 14, liver extract (343), equivalent to 4800 gm. of

liver, was given in divided doses. There were no untoward effects. The results are shown graphically in Chart II. On the third day a typical reticulocyte response began followed by a rapid rise in the red-cell count. Three days after the liver feeding there was marked subjective improvement and the stools became fewer in number. The tongue papillæ returned rapidly. Improvement thereafter continued steadily. On March 28 there was a slight drop in the blood count and another large dose of extract was given. This, as might have been expected,[5] elicited no reticulocyte response, but was followed by still further gain in blood count. The latter part of his hospital stay was complicated by a perirectal abscess which required surgical drainage. In spite of this, he left the hospital less than five weeks from the beginning of treatment feeling well and with a red cell count of nearly 4,500,000. There were only one or two brown semiformed stools daily, but there was still an excess of fat.

Discussion and Summary. The results of treatment, by liver extract, of 2 cases of sprue are reported. The diagnosis of sprue as against pernicious anemia was based on the presence of considerable amounts of free HCl in the stomach juice, the character of the stools, the absence of neurologic changes and (in 1 case) residence in the tropics. Responses similar to those usually obtained in pernicious anemia resulted, with rise in reticulocytes, increase in blood count and improvement of gastrointestinal symptoms with gain in weight and general well-being. Incidentally, it has been pointed out that the typical response may be obtained after a single large dose of liver extract as well as after daily smaller doses. The results are additional evidence of a close relationship between sprue and pernicious anemia.

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COINCIDENT DIABETES MELLITUS AND PERNICIOUS ANEMIA.

With Report of a Case.

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Reporting in 1926 the discovery of gastric achlorhydria or subacidity in a large proportion of their diabetic patients, Bowen and Aaron[1] comment upon the extreme rarity of coëxisting diabetes and primary anemia. Further, a review of the literature which I under-

took in connection with the study of the case presented below revealed only 6 case reports in which the individual was considered to have had both diseases simultaneously. The findings set down by the various authors will be summarized for comparison with the present case.

Review of Literature. Claude Bernard[2] first showed that hyperglycemia may result from repeated bleedings of dogs, yet experimental work on the interrelation of blood quality and pancreatic hormone seems not to have been carried further.

The earliest adequate case report found was that of Parkinson,[3] who in 1910 published the record of a man who came under his observation with a year's history of symptoms referable to pernicious anemia. Full physical and laboratory data indicated a well-advanced stage of the disease. Glycosuria was not present. The patient proceeded to enter upon a remission under a regime including high-protein, high-caloric diet, hydrochloric acid and arsenic. Five months later he was readmitted to the hospital with ten days of symptoms of profound anemia and of diabetes. Urinalysis showed 5 per cent sugar, later increasing amounts of acetone bodies; and the patient died five days after entry. At necropsy the pancreas was described as small, but normal microscopically; the bone marrow changes as typical of Addisonian anemia. The author expresses "little doubt that the diabetes followed on a relapse in the primary anemia," but that no anatomic changes were found to account for it.

Parkinson, speculating on the possible relation between anemia and diabetes, searched the literature to find an explanation for the low incidence of the diabetic syndrome in the face of the diminished oxygen-carrying capacity of primary anemia blood. He was able to find, he states, no mention of it in the general literature, nor "in the monographs of Addison, Byrom Bramwell or Hunter. And none in the articles of Cabot, von Noorden or French in the *Systems of Medicine*."

In a treatise on the diseases which may be associated with Addisonian anemia, Giffin and Bowler,[4] reviewing 628 anemia cases with 108 complicating diseases, mention diabetes mellitus as one such complication. Two of their anemia patients showed disturbed sugar metabolism. In one, polyuria and a blood sugar of 0.27 per cent developed; in a second instance, transient glycosuria was found. These authors, too, mention the fact that glycosuria, if not true diabetes, may be secondary to anemia, possibly as a result of a deficient oxygen supply.

A third instance of the association was furnished by Schumann[5] who detailed the findings in a woman, aged fifty-five years, who had pernicious anemia. In this patient, the central nervous system symptoms were marked: insomnia, girdle sensation, tingling and numbness of hands and feet. In addition, routine urinalysis showed a large amount of sugar; blood sugar was 0.222 per cent. The

blood Wassermann test was negative. The hemoglobin was 35 per cent; erythrocytes, 1.2 millions; leukocytes, 6400; the stained film showed much anisocytosis and poikilocytosis. There was no evidence of bleeding in the gastrointestinal tract.

With exclusion of foods containing sugar, and a daily small dose of insulin, the patient's glycosuria disappeared in ten weeks. Subsequently, sugar-containing foods were permitted without recurrence of the diabetes. The anemia picture "ran the usual course," and transfusions were given for a time. The report does not mention gastric acid findings or remissions in the anemia.

Two of the 3 cases reported recently by Adams[6] were particularly clear-cut. One patient, a woman, aged forty-five years, was first diagnosed as anemic in 1912. Symptoms were indefinite, findings suggested splenic anemia. She was followed fairly closely until 1923, during which years the spleen remained enlarged. In that year, 8.2 per cent of urinary sugar was discovered, the first suggestion of diabetes. The latter was easily controlled, however, without insulin, and did not interfere with removal, early in 1923, of hemorrhoids which had bled intermittently. Paresthesias appeared in December, 1923, and a month later, the patient was found on readmission, to have a severe anemia of the Addison type, along with hyperglycemia. The hyperglycemia was removed with insulin, and she went home, where she gave up insulin, and returned two months later in diabetic coma. Large amounts of insulin (total, 230 units within twelve hours) failed to bring the blood sugar below 0.40 per cent, and death occurred the day following entry. Necropsy showed atrophy of the pancreas, with "hyalo-fibrinoid changes in the islands." The bone marrow was gray-red in color, containing a moderate number of megaloblasts, numerous normoblasts and eosinophils.

Adams describes a second woman, aged fifty-six years, who gave a history of mild diabetes. Onset of sore mouth and tongue occurred eight years later; paresthesias two months prior to entry. Examination revealed an atrophic tongue, diminished vibratory sense in the lower extremities. Stomach contents contained no free HCl. Fasting blood sugar was 0.23 per cent. The color index was 1 or slightly under; there was moderate variation in size and shape of the erythrocytes in the stained film.

The same author refers to a third case in the series of 1000 primary anemias and 2000 diabetics, which he reviewed. This patient, a diabetic of long standing, developed primary pernicious anemia while under the care of another physician. Further data were not obtained.

In the above reports, the criteria for the diagnosis of primary pernicious anemia vary. The reviewer consequently cannot be certain in the cases which failed to come to autopsy that the pernicious anemia was the clinical entity, or was possibly a severe

CHRONOLOGICAL OUTLINE OF CASE OF C. L. TO SHOW PROGRESS OF DIABETES AND PERNICIOUS ANEMIA.

Date.	Symptoms.	Hemoglobin per cent.	Erythrocytes in millions.	Urine sugar.	Fasting blood sugar, gm. in 100 cc.	Treatment.	Remarks.
May 5, 1925	Weakness, giddiness polydipsia, polyphagia, polyuria	...	....	"Heavily loaded"	0.228	Diet, P. 50, F. 200, C. 75, insulin 30 U.	Appeared a typical diabetic. Anemia not suspected.
Mar. 6, 1926	Tingling, numbness in hands and feet	42	1.50	0	"Normal"	5 transfusions total 2500 cc.	No evidence of diabetes. Normoblasts, aniso- and poikilocytosis in blood film.
May 7, 1926	.....	88	4.50	0	"Normal"	.....	Remission following transfusions.
Oct. 15, 1926	Weakness, vomiting, fleeting pains in arms and legs	30	1.25	0	..	Dilute HCl 1 cc. t. i. d.	Entered University Hospital. Gastric anacidity. Blood film that of pernicious anemia. No blood in stools. No evidence of diabetes.
Oct. 19, 1926	No change	30	1.75	0	..	Minot-Murphy diet started (liver 50 grams)	Indirect van den Bergh, 1 unit.
Oct. 28, 1926	Feels stronger, no gastric disturbance	42	1.75	0	..	Liver 200 grams dilute HCl 3 cc. t. i. d.	
Nov. 5, 1926	Pain in legs gone	64	2.90	..	..	.....	Leukocytes increased to normal figure.
Nov. 11, 1926	No change	70	3.25	0	0	.....	Trace albumin; several hyalin and granular casts.
Nov. 18, 1926	No change	70	3.50	..	..	.....	No excretion of neutral red by stomach glands.
Nov. 27, 1926	No symptoms	83	4.80	..	..	Carious tooth extracted	Discharged.
Jan. 3, 1927	No symptoms	93	4.40	..	..	.....	Caught cold at home, January 10, 1927.
Feb. 8, 1927	Polyuria, vomiting, pain in back	120	6.30	+ ketonuria	0.375	Intravenous glucose and insulin	Readmitted. Dehydrated. On verge of diabetic coma.
Feb. 10, 1927	.....	70	4.40	+++ ketonuria	0.375	.....	Albumin and casts.
Feb. 17, 1927	Much stronger	76	4.95	0	0.250	Diet, P. 60, F. 90, C. 80, insulin 50 U.	Occasionally mild insulin reaction.
Mar. 1, 1927	.....	87	4.10	0	0.082	Diet, P. 60, F. 160, C. 100, insulin 10 U.	Diarrhea. Trace occult blood in stools. Gastric anacidity after histamin subcutaneously.
Mar. 18, 1927	.....	71	3.90	0	0.102	Diet, P. 60, F. 160, C. 100, (approx.) Dil. HCl 2 cc. t. i. d.	No insulin. No liver. Discharged.
Nov. 18, 1927	.....	80	4.00				
April, 1928	Occasional weak and dizzy spells. Numbness continues	...	....	Occasionally present	..	Insulin 20 units daily	Takes liver once or twice a week.

secondary process due to prolonged mild bleeding. We have two completed cases, however, and must presume that the other four anemias also were of the primary type.

Case Report. C. L., white, a coal miner, aged forty-one years, was admitted to the hospital of the University of Pennsylvania, on the service of Dr. Alfred Stengel, October 14, 1926, complaining of weakness and vomiting. He had been in normal health until March, 1925, when he began to notice weakness and giddiness, excessive thirst and hunger. Two months later he was admitted to a hospital near his home, which hospital has kindly furnished a brief summary of the patient's record. Diabetes mellitus was there diagnosed upon finding glycosuria and a blood sugar of 0.228 per cent. Blood count was not made. Sugar and symptoms disappeared on a diet of 2300 calories, with daily insulin of 30 units. The patient was discharged, to return to the hospital ten months later with a history of having remained sugar-free, in spite of very irregular diet and no insulin. He had been at work in the interval.

On the second admission, blood sugar was normal, and on maintenance diet the patient showed no sugar at any time. He had developed, in the interval, however, a severe anemia, and on entry showed a hemoglobin of 42 per cent, 1.5 million erythrocytes and 4500 leukocytes. The stained film showed aniso- and poikilocytosis and normoblasts. Five transfusions of 500 cc. each served to allow his discharge after six weeks, with 4.5 million erythrocytes and 88 per cent hemoglobin. Pernicious anemia was the only diagnosis made on this second admission.

Following the second discharge the patient was able to work for only two weeks because of recurrence of weakness, dyspnea, paresthesias, sore mouth and tongue. He was referred to the hospital of the University of Pennsylvania from his home, when it was discovered that the anemia had returned to an alarming degree.

Physical examination on entry October 15, 1926, showed good development and nutrition, very pale skin and mucous membranes, with a yellowish cast. The tongue was moist, a little smooth. Heart and lungs were negative. The spleen tip was palpable. Vessel walls were soft. Reflexes were normal; vibratory sense was found diminished in the lower extremities. Rectal examination was negative. Blood pressure was 105 systolic, 60 diastolic. Temperature, pulse and respiratory rate were normal. Tentative diagnosis was primary pernicious anemia.

The significant laboratory findings are charted in the accompanying table.

There was no evidence of bleeding in the gastrointestinal tract at this time; the fluoroscopic study in a gastrointestinal Roentgen ray series, otherwise negative, gave suspicion of slight pyloric irregularity. There was no indication of kidney damage.

On a Minot-Murphy regime, in which the amount of liver was quickly raised to 200 gm. daily, the patient improved remarkably, and was discharged six weeks after entry, with a blood picture which was normal except for variation in size of the erythrocytes.

The patient kept to the liver diet at home, and was well for a month when he appeared for follow-up and further Roentgen ray study of his stomach. The blood picture remained as at time of discharge. Again, Roentgen ray was barely suggestive of hypertrophied mucosa in the pyloric region.

Shortly after this visit the patient caught cold, and in a few days began to notice polydipsia, polyuria and incontinence of urine. He lost weight and appetite, became nauseated and drowsy; and was readmitted in that

state February 8, 1927, vomiting frequently. His condition at this time was that of severe diabetic acidosis. Blood sugar was 0.375 per cent; plasma CO_2, 20 vol. per cent; and all the measures of routine acidosis care were needed to bring about recovery. When the sugar tolerance began to rise, it came back rapidly, and the patient experienced several mild hypoglycemic reactions before insulin was finally omitted entirely four weeks after entry, with a maintenance diet. The initial polycythemia shown on the chart disappeared as the dehydration was relieved; and the blood count was noted further to fall slowly. No liver was given in the diabetic trays of this period.

On this, the patient's second admission, vibratory sense was absent in the lower extremities, diminished over pelvis and spine, but present in the upper extremities and shoulder girdle. The signs of an acute nephritis, also present on admission, cleared slowly. Two readings of blood urea nitrogen were normal, and the elimination of 'phthalein by the intravenous method was 55 per cent in two hours.

A third analysis of stomach contents showed total absence of free HCl and ferments, after the ingestion of 100 cc. of 5 per cent alcohol and also after the injection of 1 cc. of $\frac{1}{1000}$ histamin subcutaneously. Stomach roentgenograms again suggesting hypertrophy of the pyloric mucous membrane, and small amounts of occult blood appearing in the stools, exploration was thought advisable by certain members of the staff who had in mind the condition simulating pernicious anemia caused by prolonged oozing from a gastrointestinal lesion. The operation was explained to the patient who decided against it. He was then discharged to the care of his local physician, slightly anemic, but symptomless, with advice to renew the liver diet on reaching home.

The patient reported by letter, after eight months, that his blood count showed 4 million erythrocytes, hemoglobin 80 per cent. He feels well most of the time, except for occasional week-long spells of weakness and dizziness. Numbness of legs and feet continues. He takes liver once or twice a week, has shown sugar in the urine from time to time and when last heard of, in April, 1928, a year after discharge, was taking 20 units of insulin daily.

Summary. 1. Six instances of diabetes associated with pernicious anemia have been found reported in the medical literature.

2. The anemia was considered the first condition to develop in 3 cases; diabetes first in 2; and in the remaining instance, both conditions were found simultaneously.

3. Necropsy findings in 2 instances confirmed the diagnoses. In the other 4, the blood picture and course of the disease were taken as evidence of pernicious anemia.

4. A case is here reported in detail, in which the diabetes evidently antedated the anemia by several months, and was not in evidence during the height of the anemia as observed in the hospital. It reappeared however, several weeks after the patient had entered a complete remission on a Minot-Murphy liver diet.

5. The diabetes, furthermore, is here mild, with two acute exacerbations, not associated with the anemic state.

6. Concerning the diagnosis of pernicious anemia, the one disturbing factor, in a clinical picture otherwise complete, is roentgenographic evidence of possible hypertrophied pyloric mucosa, which

may be bleeding slowly, although occult blood was found on only two of the many stool examinations.

7. Finally, the present study indicates, at least so far as reported clinical findings are concerned, that there exists no consistent relationship between primary pernicious anemia and diabetes. The cases so far discovered should be considered as coincidences.

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THE INTRACUTANEOUS SALT-SOLUTION TEST IN THYROTOXICOSIS.

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In 1923, McClure and Aldrich[1] first described the intracutaneous salt-solution test. They injected 0.2 cc. of 0.85 per cent aqueous solution of sodium chlorid intradermally (aseptically) into the flexor surface of the forearm, inner surface of the calf, or the lateral side of the anterior surface of the leg. A duplicate injection was made 2 cm. away. The end point of the disappearance of the elevation was determined by palpation unassisted by inspection. The raised area produced persisted for sixty minutes or more in normal cases. They found that in cases of edema there was a decided reduction of the disappearance time, the latter being roughly in inverse ratio to the degree of edema at the area of injection. In a subsequent communication,[2] the same authors reported application of the test to 16 children with generalized edema and urinary findings of albumin, casts, and red blood cells, but unassociated with nitrogen retention or evidence of cardiovascular disease. They were able to prognose with considerable accuracy the appearance and disappearance of edema, and felt that the test showed these changes earlier than any other method. It also seemed to substantiate the theory that the tissues in this type of

case are active in the development of the edema. Baker[3] studied the test in 70 cases of scarlet fever and 30 cases of diphtheria (two-thirds of whom were children) and found reduction of the disappearance time, the reduction being parallel to the severity of the intoxication.

A group of children with lobar pneumonia was tested by Harrison,[4] who found a considerable shortening of the disappearance time, with a slow return to normal after the crisis, suggesting a more persistent intoxication of the tissues than is usually considered. Lash[5] applied the test to patients with normal and toxemic pregnancies. In the latter condition there was a definitely decreased disappearance time more marked in those patients with convulsions. The degree of decrease in the disappearance time varied directly with the degree of severity of the toxemia, increasing with the general clinical improvement. Lash suggested that the test might prove of value in determining the oncoming of a toxemia earlier than by any other available method. Cohen[6] observed that intradermally-injected salt solution disappeared more rapidly from areas with deficient circulation than from those areas in which the circulation was normal, in a manner comparable to the difference observed in different parts of the body in cardiac disease. Cohen believes that the test affords a simple method of determining the level of adequate tissue oxygenation. Stern and Cohen[7] state that in all instances in which clinical circulatory deficiency exists, the disappearance time is diminished; in the area just above the seat of gangrene (existing or threatened) it is frequently as low as five minutes. In 4 myxedematous patients, Thompson[8] noted the disappearance time as being more consistently prolonged before or in the interval of thyroid omission than during the period of administration. (In all other types of edema the disappearance time has been found to be markedly diminished.) In a group of children with rheumatic heart disease and allied conditions, Olmsted[9] found that the disappearing time was normal in well-compensated nontoxic cases and in decompensation with edema shortening of the disappearance time was limited to edematous and preëdematous regions and was noted earliest in the dependent portions of the body. In these cases, the decrease in disappearance time did not precede other clinical signs of impending decompensation with sufficient constancy to make the test of much value in predicting a break in compensation. A reduced disappearance time was frequently found postoperatively by Appel and Brill,[10] who suggested this test as a method for determining the need of the tissues for water. Kunde[11] extended the study of the test to a series of adult patients with different forms of nephritis, typhoid fever, toxemias of pregnancy and other conditions, and attempted to correlate the observations with regard to the time necessary for the disappearance of the wheal with observations made with the elastometer and those made on urine and blood. By means of this test Bradford[12] found a definitely increased

avidity of the tissues for water in serum sickness Pla[13] noted a decreased disappearance time in intoxication with vomiting and diarrhea, catharsis, or any kind of ascites. The work of Feldman and Reifsneider[14] confirms the fundamental fact of the rapid disappearance of the elevation made by intradermally injected saline solution in nephritic edemas. Amitrano[15] observed that in newborn infants the cutaneous absorption of sodium-chlorid solution was invariably hastened. Recently, Feldman[16] found a decreased disappearance time in pulmonary tuberculosis.

The mechanism of the test is not entirely clear. Guggenheimer and Hirsch[17] offer a mechanical hypothesis to explain the rapid absorption of salt solution by edematous tissues. Cohen[18] and his colleagues believe that the mechanism of reaction is that of an increased affinity of the tissues for water, based largely on the work of Martin Fischer[19] who postulated that the normal turgor of a tissue depends on the physical state of its colloids and that edema results whenever the water-holding power of its colloids is increased and when a supply of free water is available. It may be that a possible difference between capillary pressure and the osmotic pressure of the blood can account for the phenomenon.

The present study comprised a series of 42 cases of thyrotoxicosis. There were 36 women and 6 men. The youngest was fourteen, the oldest sixty-nine years of age. The duration of the illness varied from one month to twenty-two years. There were 35 cases of the so-called "hyperplastic goiter" type (exophthalmic goiter) and 7 cases of "toxic adenoma." Two of the former group represented recurrences (having been previously operated upon elsewhere). The test was performed according to the original technique of McClure and Aldrich, the wheals being made on the flexor surface of the right forearm below the cubital fossa, and the end point determined by palpation. The tests were made at varying intervals before and after operation, being checked up in each case by determinations of the basal metabolic rate. A control series of injections was made in a group of nontoxic goiter patients. Care was taken to exclude from this study any case exhibiting gross cardiac or renal damage, or any acute infectious process.

It was extremely interesting to note that in every instance there was a definite decrease in the disappearance time of the intradermally injected saline solution before operation; (normally sixty minutes or more are required for the wheal made by injected salt solution to disappear). After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also returned to normal. While no exact mathematical ratio can be expressed, it may be stated that in general the more toxic the patient the more rapid the disappearance time of the wheal, and that the latter parallels the basal metabolic rate as a measure of the severity of the toxemia.

The complete protocol is presented in the accompanying table.

TABLE SHOWING AGE OF PATIENTS, DURATION OF ILLNESS, PREOPERATIVE AND POSTOPERATIVE DISAPPEARANCE TIME OF SALT-SOLUTION WHEALS WITH CORRESPONDING BASAL METABOLIC RATE DETERMINATIONS.

Case and No.	Age.	Duration.	Preoperative basal metabolic rate, plus.	Preoperative disappearance time, minutes.	Postoperative basal metabolic rate.	Postoperative disappearance time, minutes.	Type of goiter.
1. A. W.	38	2 years	56	15	−10	72	Hyperplastic.
2. S. T.	39	5 months	37	40	− 7	65	Hyperplastic.
3. M. L.	55	4 months	46	25	+15	55	Hyperplastic.
4. J. R.	28	2 years	32	48	− 3	70	Hyperplastic.
5. L. L.	20	1 year	33	37	0	60	Hyperplastic.
6. S. M.	49	9 months	30	32	−12	65	Hyperplastic.
7. H. S.	14	1 year	50	30	−10	65	Hyperplastic.
8. L. L.	50	6 weeks	40	40	−11	71	Hyperplastic.
9. R. K.	41	3 years	30	33	− 6	59	Hyperplastic recurrent.
10. A. S.	48	18 months	38	32	0	70	Adenoma.
11. H. S.	36	9 months	44	45	−11	61	Hyperplastic.
12. M. G.	60	2 years	43	35	0	58	Adenoma.
13. B. S.	52	6 months	57	27	+ 6	60	Hyperplastic.
14. E. F.	24	6 months	55	28	+ 3	59	Hyperplastic.
15. R. M.	31	7 months	55	22	+ 8	56	Hyperplastic.
16. M. N.	15	4 months	27	45	−10	62	Hyperplastic.
17. S. G.	30	4 months	36	18	−13	69	Hyperplastic.
18. M. S.	48	4 months	60	29	+ 2	61	Adenoma.
19. A. L.	21	1 year	19	50	−10	63	Adenoma.
20. G. M.	45	4 years	31	34	− 5	68	Hyperplastic.
21. R. H.	30	3 months	71	20	−10	72	Hyperplastic.
22. T. S.	38	1 month	85	17	+10	59	Hyperplastic.
23. G. R.	32	6 months	22	44	+ 3	65	Hyperplastic.
24. B. R.	34	4 years	48.5	30	− 9	68	Hyperplastic.
25. C. L.	19	3 months	51	26	− 3.5	64	Hyperplastic.
26. V. K.	33	2 months	17	48	− 4	59	Hyperplastic.
27. C. S.	32	6 months	28	45	−14	66	Hyperplastic.
28. D. G.	23	4 months	51	19	− 8.8	67	Hyperplastic.
29. G. S.	46	3 months	19	50	− 9	60	Adenoma.
30. E. G.	40	1 year	49	27	+ 8.5	60	Hyperplastic (recurrent).
31. I. P.	28	Many years	36	40	−23	78	Adenoma.
32. E. L.	34	6 months	17	55	−21	85	Adenoma.
33. A. P.	29	2 months	52	45	+ 3	65	Hyperplastic.
34. A. B.	32	18 months	35	30	− 4	66	Hyperplastic recurrent.
35. R. S.	69	6 months	66	36	+ 1.3	59	Hyperplastic.
36. F. C.	22	2 months	37	40	+ 6	61	Hyperplastic.
37. V. Z.	28	7 months	52	30	+ 1.6	66	Hyperplastic.
38. C. D.	29	4 years	33	27	+ 3.3	62	Hyperplastic.
39. J. S.	44	22 years	60	19	+ 4.4	66	Hyperplastic.
40. A. J.	27	2 months	52	25	+ 7	63	Hyperplastic.
41. R. C.	27	2 months	51	35	−26	70	Hyperplastic.
42. M. H.	31	2 months	33	37	+ 2	64	Hyperplastic.

Summary. 1. The intracutaneous salt solution test was studied in 42 cases of thyrotoxicosis, before and after operation.

2. There was a definite decrease in the disappearance time of the wheal preoperatively. After operation, with the return to normal of the basal metabolic rate and the patient's general condition, the disappearance time also became normal.

3. In a general way, the greater the toxemia, the less time was required for the wheal to disappear.

4. The disappearance time of the intradermally injected saline solution paralleled the basal metabolic rate as an index of the severity of the thyrotoxicosis.

5. The literature pertaining to this test is reviewed.

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A SIMPLE EXERCISE TOLERANCE TEST FOR CIRCULATORY EFFICIENCY WITH STANDARD TABLES FOR NORMAL INDIVIDUALS.

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For many years a variety of exercise tests have been utilized for the investigation of circulatory efficiency, including stair climbing, hopping, dumb-bell swinging, ergometer trials, and so forth. Of

these, no one method has proved entirely satisfactory, as shown by the diversity of tests suggested. Records of blood pressure, systolic and diastolic, and of pulse rate have been used most frequently as the criteria of the circulatory reactions.

As early as 1901, Mendelsohn using an ergostat, recorded the pulse changes following exercise, and Graupner, in 1906, plotted curves of blood-pressure variations after periods of muscular work.

Selig was the first to use the stair-climbing test. No quantitative measurements in foot-pounds were made, nor was the rate of running considered. Selig noted that an advantage of the stair-climbing test was the complete freedom of the thoracic movements; in other words, that there was no interference with the normal functions of the body, an advantage absent in some of the other tests.

Kahn introduced a test consisting of hopping 100 times on one foot and roughly estimated that this work averaged 3750 foot pounds.

The popularization of the dumb-bell exercise test was the work of Barringer. Dumb-bells of from 3 to 25 pounds each were used. He omitted the diastolic blood-pressure readings, as he found them of little value. He demonstrated that the amount of work necessary to produce a delayed rise in systolic blood pressure was the same whatever group of muscles was employed. Work performed with the arm and back muscles was found to give the same results as work with the thighs and legs.

Cotton, Rapport and Lewis considered not only the total amount of work done, but also the rate of work.

Rapport utilized stairs of 45 and of 90 steps respectively, each step 9 inches high, which were mounted with varying rapidity. No attempt was made in his experiments to calculate the exact amount of work performed.

Recently, Dr. May Wilson has made use of 25 and of 60 steps in an exercise tolerance test. The total heights of the steps were 15 and 30 feet respectively, and were climbed in from twenty to forty seconds. Quantitative measurements were made, but age, sex and height were not considered. Dr. Wilson also found that circulatory reactions following the stair-case and the rope-jumping tests were similar to those obtained with the dumb-bell exercise.

On a plan somewhat similar to that described in this paper, Felberbaum and Finesilver have used a test consisting of ascents of two steps, each 6 inches high. The duration of the exercise was not, however, kept constant; nor apparently were age, sex, height or weight considered; moreover, a 6-inch step seems to us too small.

In 1926, Wolffe described an ergometer which measured the work performed by the arms in rotating a disc against friction. His method may be taken as an illustration of the type of test utilized for work by upper or by lower extremities. The stationary bicycle is an example of the latter. The muscular movements involved in this type of exercise are, however, not sufficiently common for clinical use, and the psychic element may play a considerable rôle.

None of these tests, therefore, seemed exactly suitable for the purposes of the present investigation, which originated in an attempt to study variations in exercise tolerance in certain pathologic conditions. A test was desired which would: (1) permit accurate measurement of the work performed; (2) involve only an ordinary everyday muscular activity; (3) be simple enough for use in a hospital clinic or in a physician's office. Most of the tests hitherto used are applicable only to certain types of subject, so that statistics obtained with one test cannot be compared with those gained with another variety of exercise on a different type of individual. Before conclusions can be drawn from the investigation of pathologic conditions standards must be established with the same test on the normal individual.

The physician desires a test to help in diagnosing cardiac insufficiency, and to indicate improvement or the reverse in circulatory conditions. A quantitative test, applicable to all, might throw much light on the course of certain forms of heart disease.

The test we finally adopted consisted of ascending and descending two steps a variable number of times in a given period of time. Even in these days of elevators, stair climbing is work occasionally performed by everyone, so that an ascent of two steps arouses no apprehension or excitement on the part of the subject, and psychic disturbance is at a minimum. This is extremely important, since mental reactions may undoubtedly cause acceleration of the pulse rate and a rise of blood pressure, thus influencing the very factors which are to be utilized for studying the circulatory response to exercise.

This test has the further advantage of being absolutely standardizable, and of allowing exact measurement of work for patients of any weight. Dumb-bell exercises, hopping, skipping, and the like are all capable of varying interpretation according to the intelligence, vigor and goodwill of the individual patient. With stair climbing the only variation possible is in the rate of ascent and descent, a variation which is easily regulated, and which in any case appears in the final calculation of the foot-pounds of work performed.

Method of Observation. For convenience in performing the test, we devised a simple two-step contrivance made out of $\frac{3}{4}$ inch pine wood, and consisting of two steps up on one side and two down on the other, as illustrated in Fig. 1. Each step is exactly 9 inches high (and about 22 inches wide). This apparatus does not look foreboding, and moreover can be conveniently kept in the office and utilized as a seat or shelf, or placed out of the way under a table.

Blood-pressure readings were made by the auscultatory method, and heart rate was recorded by counting the radial pulsations. Both diastolic and systolic blood pressure were noted in every case, but for the purposes of this paper only the *systolic* was considered.

These observations were made first with the subject at rest in the sitting position (Fig. 2), care being taken that sufficient time should

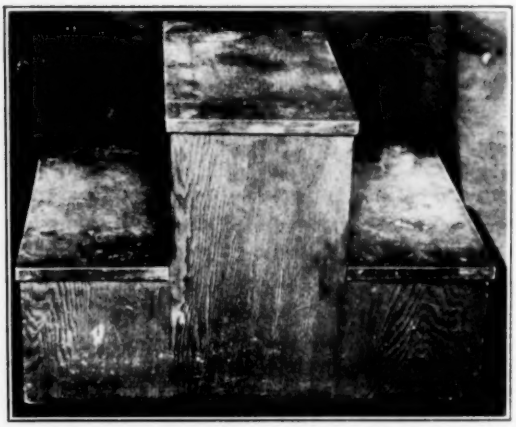

FIG. 1.—Steps for exercise tolerance test. Each step 9 inches high.

FIG. 2.—Obtaining resting blood pressure and pulse.

elapse for the circulatory conditions to reach a true resting level. In our earlier experiments, in order to eliminate mental factors as far as possible, we made a rule of always discarding the first test, and accepting only later ones. It was found, however, that a second test almost invariably gave the same results, if the first were made with the precautions suggested. This, we believe, indicates that the test produces a negligible degree of excitement.

FIG. 3.—Ready to start test.

The patient then ascended and descended the steps for a minute and a half (Figs. 3 to 12), resumed his seat, and the exact time was noted when blood pressure and pulse rate returned to their pre-exercise (resting) level. For a satisfactory performance of the test, this resting level must be reached within two minutes of the termination of the exercise. The amount of work done may, of course, be varied according to the number of ascents made in the allotted time. With each subject, therefore, we gradually increased the number of

FIG. 4.—Ascending steps.

FIG. 5.—Ascending steps.

FIG. 6.—Descending steps.

FIG. 7.—Turning to left (that is, toward the wall).

FIG. 8.—Retracing course.

FIG. 9.—Retracing course.

FIG. 10.—Turning to right (that is, toward same wall).

FIG. 11.—Commencing third ascent.

ascents until the maximum number was reached which could be accomplished without delaying the return to resting circulatory conditions beyond the prescribed two minutes. The choice of one and a half minutes as the duration of the period of exercise was made after much experimentation, which showed that a short period of more violent exercise was not so satisfactory.

FIG. 12.—Returning to desk at end of minute and a half of exercise.

The calculation of the amount of work done is simple. The individual raises himself to a height of 9 by 2 inches, or $1\frac{1}{2}$ feet, each time he mounts the steps. The work in foot-pounds at each ascent is, therefore, the product of his weight in pounds by $1\frac{1}{2}$, so that the total work is this product multiplied by the number of ascents. On the descent, there is no actual lifting of the weight against gravity. Since any work done in descending will be comparatively small in amount, and exactly proportional to the work done on the ascent, for the sake of simplicity this is omitted in the calculation. Thus, a man of 150 pounds, mounting the steps 20 times will do 150 by 20 by

$1\frac{1}{2}$, or 4500 foot-pounds of work. This is done in one and a half minutes, so that the work done in one minute will be

$$\frac{150 \times 20 \times 1\frac{1}{2}}{1\frac{1}{2}}$$

or 3000 foot-pounds per minute. Obviously, the figures $1\frac{1}{2}$ cancel each other, so that the rate of work per minute may be obtained merely by multiplying the patient's weight by the number of ascents. This is an additional advantage of fixing the period of exercise at the exact space of time of one and a half minutes.

In this way, we determined the maximum number of foot-pounds of work which could be done by normal individuals per minute, with a return to resting circulatory conditions in two minutes. In order to determine standards for different types of persons, we estimated by this method the exercise tolerance of 115 normal subjects, 59 males and 56 females, of varying weights and heights within normal limits, and of ages ranging from ten to seventy-four years. The individuals tested were chosen from many different types of occupation, but extremes such as laborers or athletes, the very obese or the abnormally thin, were excluded. Each of the cases presented was carefully investigated, and a thorough physical examination made, and in more than one-half of the subjects teleorentgenograms and electrocardiograms were taken. Any case presenting the least abnormality was excluded from the series.

Discussion of Results. From the figures of exercise tolerance thus obtained in foot-pounds of work, it appeared clear that the factors of age, sex, weight and height were of extreme importance, and must be carefully considered in any attempt to establish normal standards of work. Graphs were, therefore, plotted with foot-pounds of work as ordinates, and age (Fig. 13), weight (Fig. 14) and height (Fig. 15), respectively, as abscissæ. These curves must be considered together since the three variables of age, weight and height are so closely connected, but interesting features may be brought out by a preliminary study of each curve separately.

Considering first the graphs showing the relation between exercise tolerance and age (Fig. 13), we find that the curve for males, as would be expected, shows the steepest rise between ten and twenty years of age. A more gradual rise occurs to a maximum at about twenty-seven years, when 3795 foot-pounds of work per minute is reached. Thereafter a gradual decline occurs, and at seventy-four years the work done is only 2250 foot-pounds. Females reach a maximum of 2950 foot-pounds at about twenty-four years of age, the rise being most rapid between ten and thirteen years. It is important to note that before puberty girls are better than boys, whereas after thirteen years of age, boys take and men keep, the lead. This conclusion is also borne out by the curves for weight and height (Figs. 14 and 15).

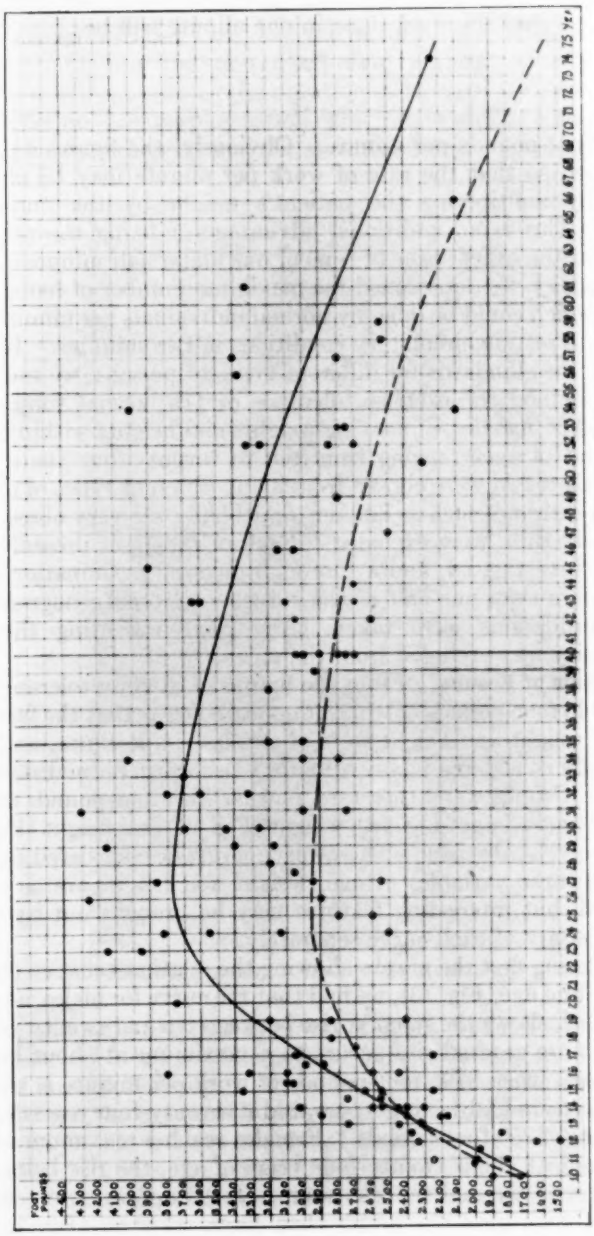

FIG. 13.—Curves of foot-pounds and ages. Full dots and line for males, small circles and broken line for females.

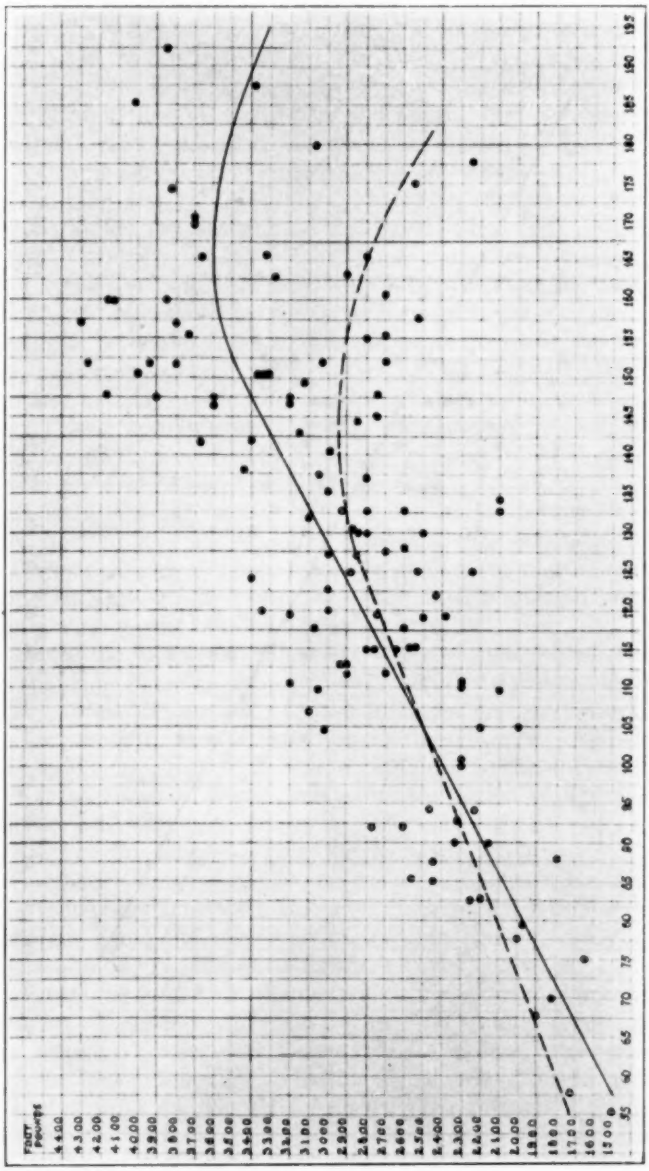

FIG. 14.—Curves of foot-pounds and weight. Full line for males, broken line for females.

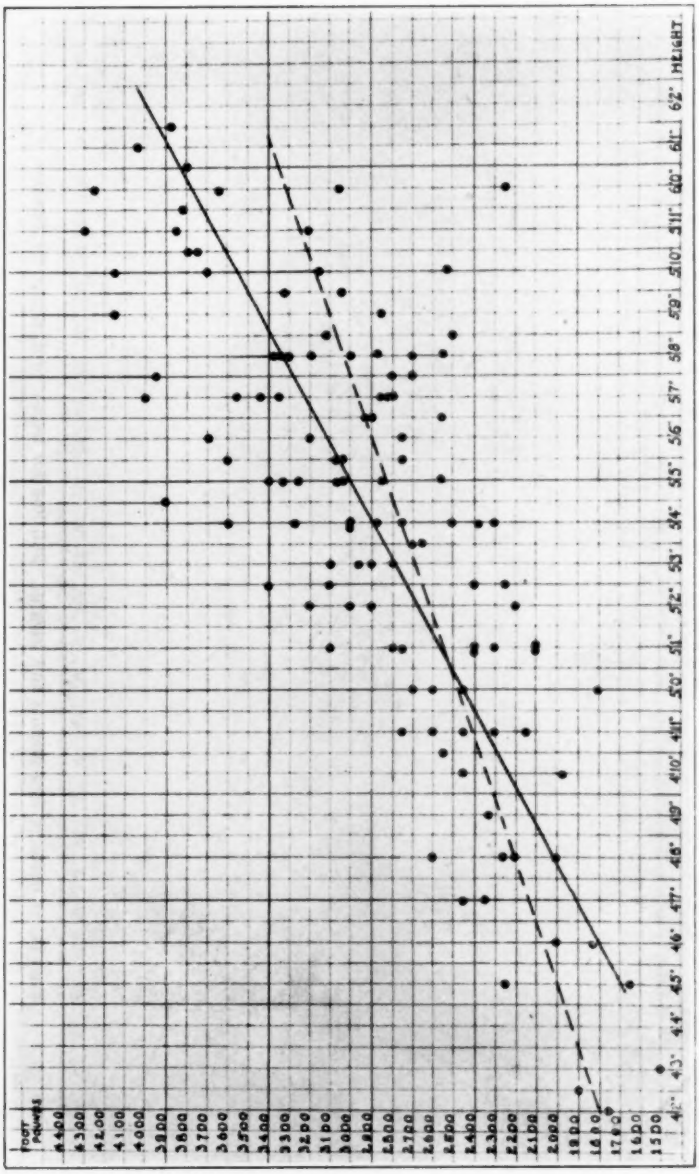

FIG. 15.—Curves of foot-pounds and height. Full line for **males**, broken line for females.

The relation between work and weight is expressed for the most part by a straight line, work capacity rising in direct proportion to increasing weight. However, after 160 to 165 pounds in men, and 135 to 145 pounds in women, there is a fall in the curve, the subjects at this weight being apparently the most efficient.

A straight line also expresses the relationship between work and height. Here the continuous rise is accounted for by the fact that taller individuals have a mechanical advantage over smaller ones in climbing a step. Males again show an advantage over females, except at the low statures of childhood, when girls do better than boys.

The steep rises in the "age" curves between ten and twenty years are clearly influenced by the great increments of weight and height during these early years. These same factors also account partly for the generally better performance of men compared with women, but not entirely, since a man always shows a higher exercise tolerance than a woman even of exactly the same weight, height and age. This is, of course, due to a greater proportion of skeletal muscle tissue per unit of body weight.

It is interesting to note that at the optimum age for this test, men have an average tolerance of about 3800, and women of about 3000 foot-pounds. That is to say, men have a work capacity of approximately $\frac{1}{2}$ horsepower, and women of about $\frac{1}{11}$, values which agree with results obtained by engineers.

Use of the Standard Tables. In order to make these data readily available as a standard test, it was essential to present them in such a form that the normal exercise tolerance for any combination of height, weight, age and sex could be obtained. The statistical treatment necessary to do this is explained in the appendix.

As the result of such treatment, the series of figures given in Tables I and II were obtained. These two tables—one for males, the other for females—give the number of foot-pounds of work arranged with regard to age and weight. Each horizontal line gives the foot-pounds of work corresponding to a particular weight at different ages, and each vertical column presents the foot-pounds corresponding to different weights at a particular age. A value can, therefore, be found for a person of either sex of any age and of any weight. To obtain variation for height a simple correction is made for individuals above and below 5 feet 4 inches. For females of all ages 25 foot-pounds are added for every inch of height above 5 feet 4 inches, and subtracted for every inch below. For men under twenty-one years, 50 foot-pounds are added or subtracted in exactly the same way. For men over twenty-one years, no correction should be made.

Since the table does not give values for every year of age, but often only for alternate years, figures for the missing ages are obtained by taking values intermediate between the figures for the years above and below.

TABLE I.—MALES. TWO-STEP EXERCISE TOLERANCE TEST.

CORRECTION FOR HEIGHT. ADD 50 FOOT-POUNDS FOR EVERY INCH ABOVE 5 FEET 4 INCHES AND SUBTRACT FOR EVERY INCH BELOW 5 FEET 4 INCHES. NO CORRECTION FOR MEN OVER TWENTY-ONE YEARS OF AGE.

Age in Years.

Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
50	2180	2225	2260	2314	2360	2426	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
52	2190	2235	2270	2325	2370	2437	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
54	2200	2245	2280	2335	2380	2447	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
56	2211	2256	2291	2346	2391	2458	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
58	2221	2266	2301	2356	2401	2468	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
60	2232	2277	2321	2366	2412	2479	2526	2586	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
62	2242	2287	2332	2377	2422	2489	2537	2596	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
64	2253	2298	2342	2387	2432	2490	2547	2607	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
66	2263	2308	2353	2398	2443	2500	2558	2617	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
68	2273	2319	2363	2408	2453	2510	2568	2628	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
70	2284	2329	2374	2419	2464	2521	2578	2638	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
72	2294	2339	2384	2429	2474	2531	2587	2650	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
74	2305	2350	2395	2440	2485	2542	2599	2659	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
76	2315	2360	2405	2450	2495	2552	2609	2670	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
78	2325	2371	2416	2461	2506	2563	2620	2680	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
80	2336	2381	2426	2471	2516	2573	2630	2690	2755	2844	2900	2945	2985	3023	3001	2950	2909	2859	2809	2758	2707	2657	2607	2545	2495	2444	2394	2343	2292	2242	2191
82	2346	2391	2436	2482	2527	2584	2641	2701	2765	2854	2910	2960	3006	3044	3021	2970	2920	2879	2829	2778	2727	2677	2627	2566	2515	2464	2414	2363	2313	2262	2212
84	2357	2402	2447	2492	2537	2594	2651	2711	2775	2864	2923	2976	3026	3064	3041	2991	2940	2899	2849	2798	2748	2697	2648	2586	2535	2485	2434	2384	2333	2282	2232
86	2367	2412	2457	2502	2548	2605	2662	2722	2786	2875	2936	2992	3046	3084	3062	3011	2960	2910	2860	2819	2768	2717	2668	2606	2556	2405	2455	2404	2353	2303	2252
88	2378	2423	2468	2513	2558	2615	2672	2732	2796	2885	2949	3009	3067	3105	3082	3031	2981	2930	2880	2839	2788	2738	2688	2627	2576	2525	2475	2424	2374	2323	2273
90	2388	2433	2478	2523	2568	2626	2683	2743	2807	2896	2963	3026	3087	3125	3102	3052	3001	2951	2900	2859	2809	2758	2708	2647	2590	2546	2495	2445	2394	2343	2293
92	2399	2444	2489	2534	2579	2636	2693	2753	2817	2906	2976	3043	3107	3145	3123	3072	3021	2971	2921	2870	2829	2779	2729	2667	2617	2566	2516	2465	2414	2364	2313
94	2409	2454	2499	2544	2589	2646	2703	2764	2828	2917	2990	3061	3128	3166	3143	3092	3042	2991	2941	2890	2849	2799	2749	2688	2637	2586	2536	2485	2435	2384	2333
96	2419	2465	2510	2555	2600	2657	2714	2774	2838	2927	3003	3078	3148	3186	3163	3113	3062	3011	2961	2910	2860	2819	2769	2708	2657	2607	2556	2506	2455	2404	2354
98	2430	2475	2520	2565	2610	2667	2724	2784	2849	2938	3017	3095	3168	3206	3184	3133	3082	3033	2982	2931	2880	2839	2789	2728	2678	2627	2576	2526	2475	2425	2374
100	2440	2485	2531	2576	2621	2678	2735	2795	2859	2948	3030	3113	3188	3226	3204	3152	3103	3052	3002	2951	2900	2850	2800	2749	2698	2647	2597	2546	2496	2445	2394
102	2451	2496	2541	2586	2631	2688	2745	2800	2869	2959	3044	3130	3208	3247	3224	3174	3123	3072	3022	2971	2921	2870	2820	2769	2718	2668	2617	2567	2516	2465	2415
104	2461	2506	2551	2596	2642	2699	2756	2816	2880	2969	3057	3147	3229	3267	3245	3194	3143	3093	3042	2992	2941	2890	2840	2789	2739	2688	2637	2587	2536	2486	2435
106	2472	2517	2562	2607	2652	2709	2766	2826	2890	2979	3071	3165	3249	3287	3265	3214	3164	3113	3063	3012	2961	2911	2860	2810	2759	2708	2658	2607	2557	2506	2455
108	2482	2527	2572	2617	2662	2720	2777	2837	2901	2990	3084	3182	3269	3308	3285	3235	3184	3133	3083	3032	2982	2931	2880	2830	2779	2729	2678	2628	2577	2526	2476
110	2493	2538	2583	2628	2673	2730	2787	2847	2911	3000	3097	3199	3290	3328	3306	3255	3204	3154	3103	3053	3002	2951	2901	2850	2800	2749	2698	2648	2597	2547	2496
112	2503	2548	2593	2638	2683	2740	2798	2858	2922	3011	3111	3217	3310	3348	3326	3275	3225	3174	3123	3073	3022	2972	2921	2871	2820	2769	2719	2668	2618	2567	2516
114	2513	2559	2604	2649	2694	2751	2808	2868	2932	3021	3124	3234	3330	3369	3346	3296	3245	3194	3144	3093	3043	2992	2941	2891	2840	2790	2739	2688	2638	2587	2537
116	2524	2569	2614	2659	2704	2761	2818	2878	2943	3032	3138	3251	3351	3389	3366	3316	3265	3215	3164	3114	3063	3012	2962	2911	2861	2810	2759	2709	2658	2608	2557
118	2534	2579	2625	2670	2715	2772	2829	2889	2953	3042	3151	3269	3371	3409	3387	3336	3286	3235	3184	3134	3083	3033	2982	2931	2881	2830	2780	2729	2679	2628	2577
120	2545	2590	2635	2680	2725	2782	2839	2899	2963	3053	3165	3286	3391	3430	3407	3357	3306	3255	3205	3154	3104	3053	3002	2952	2901	2851	2800	2749	2699	2648	2598
122	2555	2600	2645	2691	2736	2793	2850	2910	2974	3063	3178	3303	3412	3450	3427	3377	3326	3276	3225	3174	3124	3073	3023	2972	2922	2871	2820	2770	2719	2669	2618
124	2566	2611	2656	2701	2746	2803	2860	2920	2984	3073	3192	3321	3432	3470	3448	3397	3347	3296	3245	3195	3144	3094	3043	2992	2942	2891	2841	2790	2740	2689	2638
126	2576	2621	2666	2711	2757	2814	2871	2931	2995	3084	3205	3338	3452	3491	3468	3417	3367	3316	3266	3215	3165	3114	3063	3013	2962	2912	2861	2810	2760	2709	2659
128	2587	2632	2677	2722	2767	2824	2881	2941	3005	3094	3218	3355	3472	3511	3488	3438	3387	3337	3286	3235	3185	3134	3084	3033	2983	2932	2881	2831	2780	2730	2679

130	2597	2642	2687	2732	2777	2834	2892	2952	3016	3105	3232	3373	3493	3531	3509	3458	3407	3357	3306	3256	3205	3155	3104	3053	3003	2952	2902	2851	2800	2750	2699
132	2608	2653	2698	2743	2788	2845	2902	2962	3026	3115	3244	3391	3513	3552	3529	3478	3428	3377	3327	3276	3226	3175	3124	3074	3023	2973	2922	2871	2821	2770	2720
134	2618	2663	2708	2753	2798	2855	2912	2973	3037	3126	3256	3409	3534	3572	3549	3499	3448	3398	3347	3296	3246	3195	3145	3094	3043	2993	2942	2892	2841	2791	2740
136	2628	2674	2719	2764	2809	2866	2923	2983	3047	8136	3269	3427	3554	3592	3570	3519	3469	3418	3367	3317	3266	3216	3165	3114	3064	3013	2963	2912	2861	2811	2760
138	2639	2684	2729	2774	2819	2876	2933	2993	3058	3147	3282	3436	3574	3613	3590	3539	3489	3438	3388	3337	3286	3236	3185	3135	3084	3034	2983	2932	2882	2831	2781
140	2649	2694	2739	2785	2830	2887	2944	3004	3068	3157	3294	3464	3595	3633	3610	3560	3509	3459	3408	3357	3307	3256	3206	3155	3104	3054	3003	2953	2902	2851	2801
142	2660	2705	2750	2795	2840	2897	2954	3014	3078	3167	3307	3482	3615	3653	3631	3580	3529	3479	3428	3378	3327	3277	3226	3175	3125	3074	3024	2973	2922	2872	2821
144	2670	2715	2760	2805	2851	2908	2965	3025	3089	3178	3319	3501	3635	3674	3651	3600	3550	3499	3449	3398	3347	3297	3246	3196	3145	3094	3044	2993	2943	2892	2842
146	2681	2726	2771	2816	2861	2918	2975	3035	3100	3188	3331	3519	3655	3694	3671	3621	3570	3520	3469	3418	3368	3317	3267	3216	3165	3115	3064	3014	2963	2912	2862
148	2691	2736	2781	2826	2871	2928	2986	3046	3110	3199	3344	3537	3676	3714	3692	3641	3590	3540	3489	3439	3388	3337	3287	3236	3186	3135	3085	3034	2983	2933	2882
150	2702	2747	2792	2837	2882	2939	2996	3055	3120	3209	3356	3556	3696	3735	3712	3661	3611	3560	3510	3459	3408	3358	3307	3257	3206	3155	3105	3054	3004	2953	2903
152	2712	2757	2802	2847	2892	2949	3006	3067	3131	3221	3368	3575	3716	3755	3732	3682	3631	3581	3530	3479	3429	3378	3328	3277	3226	3176	3125	3075	3024	2973	2923
154	2722	2768	2813	2858	2903	2960	3017	3077	3141	3232	3379	3594	3737	3775	3753	3702	3651	3601	3550	3500	3449	3398	3348	3297	3247	3196	3146	3095	3044	2994	2943
156	2733	2778	2823	2868	2913	2970	3027	3087	3152	3243	3391	3614	3757	3796	3773	3722	3672	3621	3571	3520	3469	3419	3368	3318	3267	3216	3166	3115	3065	3014	2963
158	2743	2788	2834	2879	2924	2981	3038	3097	3162	3254	3402	3633	3777	3816	3793	3743	3692	3641	3591	3540	3490	3439	3389	3338	3287	3237	3186	3136	3085	3034	2984
160	2754	2799	2844	2889	2934	2991	3048	3109	3172	3267	3415	3651	3798	3836	3814	3763	3712	3662	3611	3561	3510	3459	3409	3358	3308	3257	3206	3156	3105	3055	3004
162	2764	2809	2854	2899	2945	3002	3059	3119	3183	3278	3427	3670	3818	3856	3834	3783	3733	3682	3632	3581	3530	3480	3429	3378	3328	3277	3227	3176	3126	3075	3024
164	2775	2820	2865	2910	2955	3012	3069	3129	3193	3289	3439	3688	3838	3877	3854	3804	3753	3702	3652	3601	3551	3500	3449	3398	3348	3298	3247	3196	3146	3095	3045
166	2785	2830	2875	2920	2965	3023	3080	3140	3204	3300	3452	3706	3858	3897	3875	3824	3773	3723	3672	3622	3571	3520	3470	3419	3369	3318	3267	3217	3166	3116	3065
168	2796	2841	2886	2931	2976	3033	3090	3150	3214	3312	3464	3725	3878	3917	3895	3844	3794	3743	3692	3642	3591	3541	3490	3440	3389	3338	3288	3237	3187	3136	3085
170	2806	2851	2896	2941	2986	3043	3101	3161	3225	3324	3478	3742	3899	3938	3915	3865	3814	3763	3713	3662	3612	3561	3510	3460	3409	3359	3308	3258	3207	3156	3106
172	..	..	..	..	..	..	3111	3171	3235	3335	3491	3759	3920	3958	3935	3885	3834	3784	3733	3683	3632	3581	3531	3480	3430	3379	3328	3278	3227	3177	3126
174	..	..	..	..	..	..	3122	3182	3245	3346	3504	3777	3940	3978	3956	3905	3855	3804	3753	3703	3652	3602	3551	3501	3450	3399	3349	3298	3248	3197	3146
176	..	..	..	..	..	..	3132	3192	3256	3358	3518	3794	3960	3999	3976	3926	3875	3824	3774	3723	3673	3622	3571	3521	3470	3420	3369	3318	3268	3217	3167
178	..	..	..	..	..	..	3143	3203	3266	3369	3531	3811	3981	4019	3996	3946	3895	3845	3794	3744	3693	3642	3591	3541	3490	3440	3389	3339	3288	3238	3187
180	..	..	..	..	..	..	3153	3213	3277	3381	3544	3829	4001	4039	4017	3966	3916	3865	3814	3764	3713	3663	3612	3561	3511	3460	3410	3359	3309	3258	3207
182	..	..	..	..	..	..	3164	3224	3287	3392	3558	3846	4021	4060	4037	3987	3936	3885	3835	3784	3734	3683	3632	3582	3531	3481	3430	3379	3329	3278	3228
184	..	..	..	..	..	..	3174	3234	3298	3404	3572	3863	4042	4080	4057	4007	3956	3906	3855	3804	3754	3703	3653	3602	3552	3501	3450	3400	3349	3299	3248
186	..	..	..	..	..	..	3185	3244	3308	3415	3585	3881	4062	4100	4078	4027	3977	3926	3875	3825	3774	3724	3673	3622	3572	3521	3471	3420	3369	3319	3268
188	..	..	..	..	..	..	3195	3254	3319	3426	3599	3898	4082	4121	4098	4047	3997	3946	3896	3845	3795	3744	3693	3643	3592	3542	3491	3440	3390	3339	3288
190	..	..	..	..	..	..	3206	3264	3329	3438	3612	3918	4103	4141	4118	4068	4017	3967	3916	3865	3815	3764	3714	3663	3612	3562	3511	3461	3410	3360	3309
192	..	..	..	..	..	..	..	..	..	..	..	3935	4123	4161	4139	4088	4038	3987	3936	3886	3835	3785	3734	3683	3633	3582	3532	3481	3430	3380	3329
194	..	..	..	..	..	..	..	..	..	..	..	3956	4143	4182	4159	4108	4058	4007	3957	3906	3855	3805	3754	3704	3653	3603	3552	3501	3451	3400	3350
196	..	..	..	..	..	..	..	..	..	..	..	3977	4164	4202	4179	4129	4078	4028	3977	3926	3876	3825	3775	3724	3673	3623	3572	3522	3471	3421	3370
198	..	..	..	..	..	..	..	..	..	..	..	3998	4184	4222	4200	4149	4098	4048	3997	3947	3896	3846	3795	3744	3694	3643	3593	3542	3491	3441	3390
200	..	..	..	..	..	..	..	..	..	..	..	4019	4204	4243	4220	4169	4119	4068	4018	3967	3916	3866	3815	3765	3714	3664	3613	3562	3512	3461	3411
Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60

TABLE II.—FEMALES. TWO-STEP EXERCISE TOLERANCE TEST.

CORRECTION FOR HEIGHT. ADD 25 FOOT-POUNDS FOR EVERY INCH ABOVE 5 FEET 4 INCHES AND SUBTRACT FOR EVERY INCH BELOW 5 FEET 4 INCHES.

Age in Years.

Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
50	1987	1981	1974	1967	1961	1954	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
52	2012	2006	1999	1992	1986	1979	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
54	2037	2031	2024	2017	2011	2004	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
56	2062	2056	2049	2042	2036	2029	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
58	2087	2081	2074	2067	2061	2054	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
60	2112	2106	2099	2092	2086	2079	2073	2071	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
62	2137	2131	2124	2117	2111	2104	2098	2096	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
64	2162	2156	2149	2142	2136	2129	2123	2121	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
66	2187	2181	2174	2167	2161	2154	2148	2146	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
68	2212	2206	2199	2192	2186	2179	2173	2171	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
70	2237	2231	2224	2217	2211	2204	2198	2196	2232	2263	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
72	2262	2256	2249	2242	2236	2229	2223	2221	2257	2288	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
74	2287	2281	2274	2267	2261	2254	2248	2246	2282	2313	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
76	2312	2306	2299	2292	2286	2279	2273	2271	2307	2338	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
78	2337	2331	2324	2317	2311	2304	2298	2296	2332	2363	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
80	2362	2356	2349	2342	2336	2329	2323	2321	2357	2388	2446	2580	2648	2672	2668	2642	2616	2580	2564	2538	2511	2485	2459	2433	2407	2381	2358	2329	2303	2277	2251
82	2387	2381	2374	2367	2361	2354	2348	2346	2380	2410	2466	2595	2661	2683	2678	2652	2626	2590	2573	2547	2521	2495	2469	2443	2417	2391	2365	2339	2313	2287	2260
84	2412	2406	2399	2392	2386	2379	2373	2371	2403	2432	2486	2610	2674	2694	2688	2662	2635	2609	2583	2557	2531	2505	2479	2453	2427	2401	2375	2348	2322	2296	2270
86	2437	2431	2424	2417	2411	2404	2398	2396	2426	2454	2506	2625	2687	2705	2697	2671	2645	2619	2593	2567	2541	2515	2489	2463	2437	2411	2384	2358	2332	2306	2280
88	2462	2456	2449	2442	2436	2429	2423	2422	2449	2476	2526	2640	2700	2717	2707	2681	2655	2629	2603	2577	2551	2525	2498	2473	2447	2420	2394	2368	2342	2316	2290
90	2487	2481	2474	2467	2461	2454	2448	2447	2472	2498	2546	2655	2714	2728	2717	2691	2665	2639	2613	2587	2560	2534	2508	2482	2456	2430	2404	2378	2352	2326	2300
92	2512	2506	2499	2492	2486	2479	2473	2472	2495	2520	2566	2670	2727	2739	2727	2701	2675	2649	2622	2596	2570	2544	2518	2492	2466	2440	2414	2388	2362	2336	2309
94	2537	2531	2524	2517	2511	2504	2498	2497	2518	2542	2586	2695	2740	2750	2737	2711	2685	2658	2632	2606	2580	2554	2528	2502	2476	2450	2424	2398	2371	2345	2319
96	2562	2556	2549	2542	2536	2529	2523	2522	2541	2564	2606	2705	2753	2761	2747	2720	2695	2668	2642	2616	2590	2564	2538	2512	2486	2460	2434	2408	2381	2355	2329
98	2587	2581	2574	2567	2561	2554	2548	2547	2565	2588	2626	2720	2766	2772	2757	2730	2704	2678	2652	2626	2600	2574	2548	2522	2496	2470	2444	2418	2391	2365	2339
100	2612	2606	2599	2592	2586	2579	2573	2572	2589	2608	2646	2734	2778	2782	2766	2740	2714	2688	2662	2636	2610	2583	2557	2531	2505	2479	2453	2427	2401	2375	2349
102	2637	2631	2624	2617	2611	2604	2597	2596	2613	2631	2666	2749	2790	2793	2776	2750	2724	2698	2672	2645	2619	2593	2567	2541	2515	2489	2463	2437	2411	2385	2359
104	2662	2656	2649	2642	2636	2629	2621	2620	2637	2654	2686	2764	2802	2804	2786	2760	2734	2707	2681	2655	2629	2603	2577	2551	2525	2499	2473	2447	2421	2394	2368
106	2687	2681	2674	2667	2661	2654	2645	2644	2661	2677	2706	2779	2814	2815	2796	2769	2743	2717	2691	2665	2639	2613	2587	2561	2535	2509	2483	2456	2430	2404	2378
108	2712	2706	2699	2692	2686	2679	2669	2668	2685	2700	2726	2794	2826	2825	2805	2779	2753	2727	2701	2675	2649	2623	2597	2571	2545	2518	2492	2466	2440	2414	2388
110	2737	2730	2724	2717	2711	2704	2693	2692	2709	2723	2746	2808	2837	2836	2815	2789	2763	2737	2711	2685	2659	2633	2607	2580	2554	2528	2502	2476	2450	2424	2398
112	2762	2755	2749	2742	2736	2727	2715	2718	2733	2746	2766	2823	2849	2847	2825	2799	2773	2747	2721	2695	2669	2642	2616	2590	2564	2538	2512	2486	2460	2434	2408
114	2787	2780	2774	2767	2761	2754	2740	2740	2757	2769	2786	2838	2861	2858	2835	2809	2783	2757	2731	2704	2678	2652	2626	2600	2574	2548	2522	2496	2470	2444	2418
116	2812	2805	2799	2792	2786	2778	2764	2764	2781	2792	2806	2853	2873	2869	2845	2819	2793	2766	2740	2714	2688	2662	2636	2610	2584	2558	2532	2506	2480	2453	2427
118	2837	2830	2824	2817	2811	2800	2788	2788	2805	2815	2826	2868	2885	2880	2855	2828	2802	2776	2750	2724	2698	2672	2646	2620	2595	2568	2542	2515	2489	2463	2437

120	2862	2855	2847	2840	2828	2817	2807	2808	2829	2838	2846	2883	2897	2891	2864	2838	2812	2786	2760	2734	2708	2682	2656	2630	2604	2577	2551	2525	2499	2473	2447
122	2888	2879	2870	2863	2845	2834	2826	2825	2846	2855	2863	2900	2914	2906	2878	2850	2823	2796	2770	2744	2718	2692	2666	2639	2613	2587	2561	2535	2509	2483	2457
124	2909	2902	2891	2884	2863	2851	2849	2842	2863	2872	2880	2918	2932	2922	2892	2862	2834	2806	2780	2754	2728	2701	2675	2649	2623	2597	2571	2545	2519	2493	2467
126	2932	2925	2908	2901	2883	2873	2866	2859	2880	2889	2897	2936	2950	2938	2906	2874	2845	2816	2790	2764	2737	2711	2685	2659	2633	2607	2581	2555	2529	2503	2476
128	2952	2945	2924	2918	2903	2892	2883	2876	2897	2906	2914	2954	2968	2954	2920	2886	2856	2825	2799	2773	2747	2721	2695	2669	2643	2617	2591	2565	2538	2512	2486
130	..	..	2942	2935	2925	2914	2900	2893	2914	2923	2931	2972	2986	2970	2934	2897	2866	2835	2809	2783	2757	2731	2705	2679	2653	2627	2600	2574	2548	2522	2496
132	..	..	2950	2952	2942	2931	2917	2910	2931	2940	2948	2990	3004	2986	2948	2909	2877	2845	2819	2793	2767	2741	2715	2689	2662	2636	2610	2584	2558	2532	2506
134	..	..	2976	2969	2959	2948	2934	2927	2948	2957	2965	3007	3022	3002	2962	2921	2888	2855	2829	2803	2777	2751	2724	2698	2672	2646	2620	2594	2568	2542	2516
136	..	..	2993	2986	2976	2965	2951	2944	2965	2974	2982	3025	3040	3018	2976	2933	2899	2865	2839	2813	2786	2760	2734	2708	2682	2656	2630	2604	2578	2552	2526
138	..	..	3013	3003	2993	2982	2968	2961	2982	2991	2999	3043	3058	3034	2990	2944	2910	2875	2848	2822	2796	2770	2744	2718	2692	2666	2640	2614	2588	2562	2535
140	..	..	..	..	3010	2999	2985	2978	2999	3008	3016	3061	3076	3050	3004	2956	2920	2884	2858	2832	2806	2780	2754	2728	2702	2676	2650	2624	2597	2571	2545
142	..	..	..	..	3027	3016	3002	2995	3016	3025	3033	3079	3094	3066	3018	2968	2931	2894	2868	2842	2816	2790	2764	2738	2712	2686	2659	2633	2607	2581	2555
144	..	..	..	..	3044	3033	3019	3012	3033	3042	3050	3097	3112	3082	3032	2980	2942	2904	2878	2852	2826	2800	2774	2748	2721	2695	2669	2643	2617	2591	2565
146	..	..	..	..	3061	3050	3036	3029	3050	3059	3067	3115	3130	3098	3046	2992	2953	2914	2888	2862	2836	2810	2783	2757	2731	2705	2679	2653	2627	2601	2575
148	..	..	..	..	3078	3067	3053	3046	3067	3076	3084	3132	3148	3114	3060	3004	2964	2924	2898	2872	2845	2819	2793	2767	2741	2715	2689	2663	2637	2611	2585
150	..	..	..	..	..	..	3070	3063	3084	3093	3101	3150	3166	3130	3074	3016	2975	2934	2907	2881	2855	2829	2803	2777	2751	2725	2699	2673	2647	2620	2594
152	..	..	..	..	..	..	3087	3080	3101	3110	3118	3168	3184	3146	3088	3028	2985	2943	2917	2891	2865	2839	2813	2787	2761	2735	2709	2682	2656	2630	2604
154	..	..	..	..	..	..	3104	3097	3118	3128	3135	3186	3202	3162	3102	3040	2996	2953	2927	2901	2875	2849	2823	2797	2771	2744	2718	2692	2666	2640	2614
156	..	..	..	..	..	..	3121	3114	3135	3145	3152	3202	3220	3178	3116	3052	3007	2963	2937	2911	2885	2859	2833	2806	2780	2754	2728	2702	2676	2650	2624
158	..	..	..	..	..	..	3138	3131	3152	3162	3169	3219	3238	3194	3130	3064	3018	2973	2947	2921	2895	2868	2842	2816	2790	2764	2738	2712	2686	2660	2634
160	..	..	..	..	..	..	..	3148	3169	3179	3186	3237	3256	3210	3144	3076	3029	2983	2957	2930	2904	2878	2852	2826	2800	2774	2748	2722	2696	2670	2644
162	..	..	..	..	..	..	..	3165	3186	3196	3203	3255	3274	3226	3158	3088	3040	2993	2966	2940	2914	2888	2862	2836	2810	2784	2758	2732	2706	2680	2653
164	..	..	..	..	..	..	..	3182	3203	3213	3220	3273	3292	3242	3172	3100	3050	3004	2976	2950	2924	2898	2872	2846	2820	2794	2768	2741	2715	2689	2663
166	..	..	..	..	..	..	..	3199	3220	3230	3237	3291	3310	3258	3186	3112	3061	3015	2986	2960	2934	2908	2882	2856	2830	2803	2777	2751	2725	2699	2673
168	..	..	..	..	..	..	..	3216	3237	3247	3254	3308	3328	3274	3200	3124	3072	3026	2996	2970	2944	2918	2892	2865	2839	2813	2787	2761	2735	2709	2683
170	..	..	..	..	..	..	..	3233	3254	3264	3271	3326	3346	3290	3214	3136	3083	3037	3006	2980	2954	2927	2901	2875	2849	2823	2797	2771	2745	2719	2693
172	..	..	..	..	..	..	..	3250	3271	3281	3288	3344	3364	3306	3228	3148	3094	3048	3016	2989	2963	2937	2911	2885	2859	2833	2807	2781	2755	2729	2703
174	..	..	..	..	..	..	..	3267	3288	3298	3305	3362	3382	3322	3242	3160	3105	3059	3025	2999	2973	2947	2921	2895	2869	2843	2817	2791	2765	2738	2712
176	..	..	..	..	..	..	..	3284	3305	3315	3322	3380	3400	3338	3256	3172	3115	3070	3035	3009	2983	2957	2931	2905	2879	2853	2827	2800	2774	2748	2722
178	..	..	..	..	..	..	..	3301	3322	3332	3339	3398	3418	3354	3270	3184	3126	3081	3045	3019	2993	2967	2941	2915	2889	2862	2836	2810	2784	2758	2732
180	..	..	..	..	..	..	..	..	..	..	..	3415	3436	3370	3284	3196	3137	3092	3055	3029	3003	2977	2951	2924	2898	2872	2846	2820	2794	2768	2742
182	..	..	..	..	..	..	..	..	..	..	..	3433	3454	3386	3298	3208	3148	3103	3065	3039	3013	2986	2960	2934	2908	2882	2856	2830	2804	2778	2752
184	..	..	..	..	..	..	..	..	..	..	..	3451	3472	3402	3312	3220	3159	3114	3075	3048	3022	2996	2970	2944	2918	2892	2866	2840	2814	2788	2761
186	..	..	..	..	..	..	..	..	..	..	..	3469	3490	3418	3326	3232	3170	3125	3084	3058	3032	3006	2980	2954	2928	2902	2876	2850	2823	2797	2771
188	..	..	..	..	..	..	..	..	..	..	..	3487	3508	3434	3340	3244	3180	3135	3094	3068	3042	3016	2990	2964	2938	2912	2885	2859	2833	2807	2781
190	..	..	..	..	..	..	..	..	..	..	..	3505	3526	3450	3354	3256	3191	3145	3104	3078	3052	3026	3000	2974	2947	2921	2895	2869	2843	2817	2791
Weight	10	11	12	13	14	15	16	17	18	19	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60

Thus for a boy, aged fourteen years, weighing 104 pounds the table will show a figure of 2642 foot-pounds. A height, let us say, of 5 feet 5 inches means 1 inch above the standard 5 feet 4 inches and therefore an addition of 50 foot-pounds, giving a total of 2692. A woman, aged forty-seven years, weighing 130 pounds, and 5 feet 2 inches tall, should be able to perform 2616 foot-pounds of work. That is, taking the mean between the figures for forty-six and forty-eight years, we obtain 2666 by age and weight from the table, then deduct 2 by 25, or 50, as a correction for a height 2 inches below the standard, giving a total of 2616 foot-pounds.

A deviation of 10 per cent in either direction may be regarded as still within normal limits.

Method of Performing Test. The steps (Fig. 1), a watch—preferably a stop-watch—and a blood-pressure instrument are all the apparatus required. Correct figures for the patient's height, weight and age are ascertained, and the normal number of foot-pounds of work to be expected are obtained from the tables as described above. This number is divided by the patient's weight, the quotient being the number of ascents he should make in a minute and a half. Thus a boy, aged fourteen years, as noted above, weighing 104 pounds and five feet five in height would be expected from the tables to do 2692 foot-pounds of work: he should, therefore, make

$$\frac{2692}{104}$$

or 26 ascents. The patient is seated, and rests until his pulse and blood pressure fall no lower, as indicated by repeated observations (Fig. 2). This may require from three to five minutes. The blood-pressure cuff is allowed to remain on the arm, and the patient stands ready in front of the steps. At a given signal, the exact time being carefully noted, and most conveniently taken at a whole or half minute, he ascends the steps. He descends on the other side, and returns, ascending the steps again and descending to his original starting point. This is repeated until his allotted number of ascents has been completed in the one and a half minutes (Figs. 3 to 12). The turn before each ascent should always be made toward the same side of the room, to insure an alternation of turn to right and left. This is to prevent giddiness or vertigo, factors which produce marked changes in pulse and blood pressure. The patient is kept to the correct rate of stair climbing by observation of the time during the exercise, his rate being accelerated or retarded as may be necessary to complete his quota of ascents in the allotted time. Our procedure has been to allow the last five or six seconds of the exercise time for the subject to resume his seat. Blood pressure and pulse readings are then again taken as often as desired. If the individual is normal, and there is no complicating factor such as a cold, men-

strual period or headache, the pulse rate and blood pressure will return to normal within two minutes. Although we have watched for dyspnea, cyanosis and fatigue, we have found that this test causes few, if any signs of discomfort, since it involves merely an habitual activity. It is worthy of note, however, that in patients with valvular or muscular disease of the heart, these objective signs become very prominent.

A return of the pulse to a rate within five beats of that before exercise, and of the blood pressure to a level within 5 mm. of Hg. is accepted as a normal response.

Method for Obtaining Patient's Maximum Tolerance. If the blood pressure does not return to resting level within the two minutes the patient's tolerance is subnormal. If the exact exercise tolerance of the individual is desired, the test should be repeated using fewer ascents until a number is reached which permits a return within the prescribed time. On the other hand, if the blood pressure and pulse rate return to the resting level sooner than two minutes, the exercise tolerance is above average, and the number of ascents should be increased.

The product of the number of ascents by the weight of the individual gives the foot-pounds of work performed per minute.

By the careful use of this test the physician may discover the early stages of circulatory insufficiency, or may trace the progress of an organic condition of the heart or the degree of recovery from such an insufficiency. The quantitative information obtained may be used in giving advice as to general physical activity, or sports and games. The foot-pounds of work performed by patients with valvular or myocardial disease may be studied and the insufficiency thus graded.

Summary. The advantages of a quantitative method for an exercise tolerance test are described, and its value in diagnosis emphasized.

The test here described is an extremely simple one, utilizes habitual muscular movements, causing a minimum of excitement, and no dizziness or vertigo. It consists in ascending and descending two steps, each 9 inches high. The number of foot-pounds of work performed is easily calculated.

The criterion for the satisfactory performance of the test is a return of systolic blood pressure and of pulse rate to the preëxercise (resting) level within two minutes after the end of exercise.

Tables have been constructed giving foot-pounds of work per minute performed by normal individuals, with variations for sex, age, height and weight.

Curves of foot-pounds of work per minute, plotted against age, show that until about puberty girls perform more efficiently than boys, but after thirteen years males do better than females. The sharpest rise in the curve occurs between ten and twenty years of

age. Males reach a maximum of about 3795 foot-pounds of work at twenty-six to twenty-nine years, and women a maximum of 2950 at about twenty-four years. After these optimum ages a gradual but steady decline occurs.

Men at the optimum age have a work capacity of about $\frac{1}{8}$ horsepower, and women about $\frac{1}{11}$.

Exercise tolerance varies directly with body weight up to the optimum weight of 160 to 165 pounds for men, and 135 to 145 pounds for women. Beyond these weights the exercise tolerance falls.

The relation of work capacity to height is a direct one; the taller the individual the greater is his exercise tolerance.

The practical importance of the procedure is that the patient can be tested to determine: (1) whether his exercise tolerance is within normal limits, (2) what his actual maximal tolerance is in foot-pounds.

The test is helpful in the diagnosis and the grading of circulatory efficiency and insufficiency, and for tracing the changes arising therefrom during the progress of an organic condition of the heart, or during recovery. It may also be used in giving advice as to sports and games.

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APPENDIX.

Statistical Treatment of Data for Construction of Tables.

BY F. C. CHILLRUD.

THE purpose of the statistical treatment of the data was to combine measurements to indicate best what one might expect the score in foot-pounds to be for the various combinations of height, weight and age in each of two groups (59 males and 56 females).

Partial correlation and regression equation technique was not applicable as a curvilinear relationship existed between age and each of the other

variables. A second or higher degree parabola was tried but abandoned. Finally, study of the various correlation tables resulted in breaking up each group into two parts, those below and those above twenty-one years of age, and using the ordinary partial and regression equation technique, which fitted fairly well for these straight lines. The resulting regression equations were:

Males, below twenty-one years of age, 22 cases. Foot-pounds = 54.4 (height) + 5.22 (weight) + 45.1 (age) − 2017.

Males, above twenty-one years of age, 37 cases: Foot pounds = −4.8 (height) + 10.2 (weight) − 25.3 (age) + 3203.

Females, below twenty-one years of age, 26 cases: Foot-pounds = 24.7 (height) + 12.5 (weight) − 6.59 (age) − 153.

Females, above twenty-one years of age, 30 cases: Foot-pounds = 25.3 (height) + 4.9 (weight) − 13.0 (age) + 1022.

To secure the values found in Tables I and II, 5 feet 4 inches was substituted for height in all of the above equations; they were then solved in foot-pounds for the varying values of weight and age specified in the tables. Discrepancies, however, were found between the values in the neighborhood of ages twenty and twenty-two years in the case of both tables, due to the fact that values for twenty years and below were calculated from one equation and those for twenty-two years and above from another. A smoothing process was employed to bring the two parts of each table together at this point.

The following table gives a summary of the means, standard deviations and correlation coefficients obtained in the case of each of the four groups. The table also affords a comparison of the standard deviation of foot-pounds in the case of each group with the standard error of estimate in predicting foot-pounds from a combination of measurements of height, weight and age. In order to conserve space, no figures for probable errors of the means, standard deviations and correlation coefficients are included.

Means.

	Males.		Females.	
Means.	Below 21.	Above 21.	Below 21.	Above 21.
Foot-pounds	2815.0	3430.0	2331.0	2810.0
Height	64.7	68.2	57.4	64.4
Weight	119.8	156.7	92.4	129.8
Age	15.1	40.6	13.7	36.6
Standard Deviations.				
Foot-pounds	522.0	514.7	379.5	350.0
Height	4.56	2.77	4.0	2.91
Weight	23.2	13.8	17.4	17.1
Age	2.36	13.0	2.22	10.3
Correlation Coefficients.				
Foot-pounds and height	0.847	0.241	0.722	0.393
Foot-pounds and weight	0.802	0.257	0.765	0.270
Foot-pounds and age	0.770	−.632	0.645	−.383
Height and weight	0.877	0.483	0.863	0.456
Height and age	0.825	−.211	0.819	−.192
Weight and age	0.751	0.006	0.823	0.172
Standard deviation (foot-pounds)	522.0	515.0	379.0	350.0
Standard error of estimate in predicting foot-pounds	263.0	375.0	240.0	294.0

THE WATER BALANCE IN CARDIAC DECOMPENSATION.

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Edema is one of the outstanding signs of decompensation. Loeb[1] has thus summarized the present status of the knowledge of this circumstance: "Dilatation of the capillaries and veins due to the faulty functioning of the circulation is the principal cause of the increased transudation and the subsequent edema in cardiac decompensation, but there may perhaps be in addition an increased filtration pressure responsible for these results. The vascular dilatation is apparently followed by an increased permeability of the capillaries and by a movement of sodium chlorid and water in the direction from the blood to the tissues. Retention of sodium chlorid plays a rôle also in the case of cardiac edema, although it is a smaller one than in the case of renal edema. In certain stages of cardiac edema a hydremia seems to occur. As to the occurrence of a true plethora, the statements are contradictory. In addition to the increased transudation, there is a delayed absorption and an alteration in the relations determining the exchange of fluid between tissues and blood vessels. Experimentally produced myocarditic lesions may give rise to a lowering of blood pressure and a diminution in the amount of urine under certain conditions, but so far it has not been possible to influence by this experimental method the amount of edematous fluid."

The importance of the kidney in the elimination of the edematous fluid is clearly admitted. The work of Richards[2] established the changes in glomerular activity with variations in blood pressure and the existence of an optimal pressure for glomerular filtration. Furthermore, Clark[3] and Eyster and Middleton[4] determined a definite relationship between venous pressure and urinary output in certain cases of cardiac decompensation. As the venous pressure falls, diuresis ensues and *vice versa*. This inverse ratio of venous pressure to urinary output is by no means constant, but its occurrence is frequent enough to arrest the attention. Sollmann's observation[5] of a probable obliteration of the filtration space in Bowman's capsule on the elevation of the venous pressure may supplement the earlier explanation of a compression of the tubules. His pressure readings, however, exceed the limits of clinical observation in the peripheral veins.

With such significant circulatory relationships, the kidney occupies an important position in reflecting the cardiovascular competency.

It has, of course, been remarked that the water balance gives valuable information in cardiac decompensation, but the prognostic importance of its routine study is not generally recognized in practice. Obviously, the fluid intake and the fluid lost by other channels than the kidneys will directly affect the urinary output. Beyond this, Addis and Watanabe[6] showed a surprising range of urinary output in different individuals on a fixed fluid intake, and indeed in the same person on different days or in different parts of the same day. From many sources Weir, Larson and Rowntree[7] adduced the following figures for the average intake and urinary output of fluids:

Intake	2290 to 3700 cc.
Urinary output	1500 to 2000 cc. (65 to 54 per cent).

It may be stated then that the urinary output represents approximately 60 per cent of the fluid intake. This figure is of necessity a very arbitrary one: and subject to the loosest construction, any increase of the output above this point may be termed diuresis.

TABLE I.—DAILY DISTRIBUTION OF THE DECOMPENSATED CASES ACCORDING TO OUTPUT-INTAKE FIGURES.

Days		1.		2.		3.		4.		5.		6.		7.		8.		9.	
Termination		S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Output-intake ratio.	100%	6	5	5	10	12	10	15	7	15	10	12	7	12	8	14	7	7	4
	80	1	4	2	3	3	3	4	5	3	6	6	2	4	5	4	7	3	3
	60	4	4	8	5	7	3	7	6	5	4	6	8	9	8	8	4	14	8
	40	4	6	6	5	8	8	7	10	8	10	6	11	8	8	6	7	5	9
	20	5	4	6	8	7	5	5	6	7	4	8	3	2	7	7	7	6	5
	1	0	7	0	3	1	5	1	2	2	4	0	4	1	2	1	2	2	3

S., surviving; D., dying.

(*Continued.*)

Days		10.		11.		12.		13.		14.		15.		16.		17.		18.	
Termination		S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.	S.	D.
Output-intake ratio.	100%	5	6	10	5	3	4	7	3	8	3	7	4	5	3	4	4	5	3
	80	6	2	3	2	5	1	6	2	7	3	3	3	2	0	6	1	5	2
	60	12	5	9	8	10	7	6	7	10	3	11	5	13	6	10	1	7	2
	40	8	8	5	6	10	10	10	8	8	8	11	4	7	4	10	9	7	6
	20	4	6	6	4	6	1	8	4	3	6	3	7	4	4	3	4	6	2
	1	2	3	6	4	1	3	0	2	3	0	0	1	2	4	0	1	2	1

S., surviving; D., dying.

As a matter of routine the fluid intake and output of all decompensated cardiac cases have been charted since the opening of the Wisconsin General Hospital in 1924. The Karell diet modified to include 36 ounces (1080 cc.) of milk daily is the common order on admission. No effort has been made to estimate the amount of fluid derived from other food added from time, to time since a clinical procedure available to the general practitioner is sought. Unfor-

TABLE II.—ANALYSIS OF THE WATER BALANCE IN CARDIAC DECOMPENSATION.

Day		1.				2.				3.				4.				5.				6.			
Termination		S.		D.		S.		D.		S.		D.		S.		D.		S.		D.		S.		D.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Output-intake ratio.	Above 60%	11	55.0	13	43.3	15	55.0	18	52.9	22	57.8	16	47.0	26	66.6	18	50.0	23	57.5	20	52.6	24	63.1	17	48.5
	Below 60%	9	45.0	17	56.6	12	45.0	16	47.0	16	42.1	18	52.0	13	33.3	18	50.0	17	42.5	18	47.3	14	36.9	18	51.4

Day		7.				8.				9.				10.				11.				12.			
Termination		S.		D.		S.		D.		S.		D.		S.		D.		S.		D.		S.		D.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Output-intake ratio.	Above 60%	25	69.4	21	55.2	26	65.0	18	52.9	24	64.8	15	46.8	23	62.1	13	43.3	22	56.4	15	51.7	18	51.4	12	46.1
	Below 60%	11	30.5	17	44.7	14	35.0	16	47.0	13	35.1	17	53.1	14	37.8	17	56.6	17	43.5	14	48.2	17	48.5	14	53.8

Day		13.				14.				15				16.				17.				18.			
Termination		S.		D.		S.		D		S.		D.		S.		D.		S.		D.		S.		D.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Output-intake ratio.	Above 60%	19	51.3	12	46.1	25	64.1	9	39.1	21	60.0	12	50.0	20	60.6	9	42.8	20	60.6	6	30.0	17	53.1	7	43.7
	Below 60%	18	48.6	14	53.8	14	35.8	14	60.8	14	40.0	12	50.0	13	39.3	12	57.1	13	39.3	14	70.0	15	46.8	9	56.2

S., surviving; D., dying.

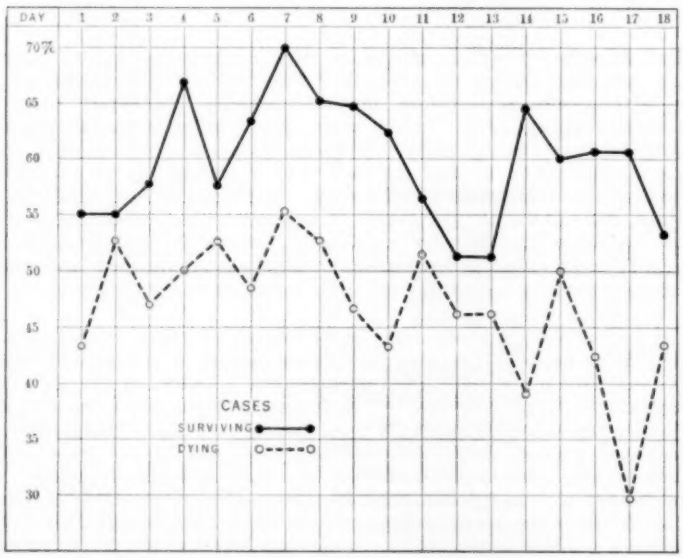
tunately, no scales have been available to add the further data of weight changes in these bed cases. A total of 108 instances of cardiac decompensation with adequate data for the present purposes has been studied in that period. They lend themselves readily to the following division:

	Surviving.	Dying.
Edematous	46	45
Nonedematous	13	4
	59	49

For the study of the water balance the edematous cases (91) alone have been considered.

In Table I, the actual number of cases falling under the various output-intake ratios is entered for each of the first eighteen days of hospitalization. In Table II, these cases have been gathered into two groups, those showing above 60 per cent output and those below 60 per cent, the arbitrary level of diuresis. To clarify further these figures the percentages are stated for the surviving and the dying groups on the separate days. Chart I reduces these percentage figures

CHART I.



to a graph in which the proportions of the studied cases of the two groups showing diuresis on the several days are plotted. Strikingly the fatal group shows a majority of its components exceeding the 60 per cent output-intake figure on but seven of the eighteen days, whereas the surviving group showed a constant majority with diuresis for any given day. Attention is directed to the rough

S., surviving; D., dying.

similarity of the form of the two curves in the first thirteen days of residence. In this period, six of the seven days of preponderance of diuresis in the fatal group occurred. In both groups, the curves have an upward swing in the first week and thereafter a sharp decline. With the close of the second week and the beginning of the third week the curves diverge.

These data indicate a distinct tendency for a primary diuresis in all cases of decompensation with edema under the circumstances of hospital care. This tendency is less marked and less sustained in the fatal group. Occasionally the primary period of diuresis does not make its appearance in the fatal cases, and in only a few instances is the curve of output-intake maintained at a satisfactory level in this group. As a rule even the surviving cases show a slump in the curve of diuresis after the primary rise, but characteristically there is an early recovery of a sound output-intake ratio. Clearly no arbitrary rules based on the available data are admissible. Nevertheless a simple and safe barometer of circulatory efficiency is offered in the study of the water balance in cardiac decompensation.

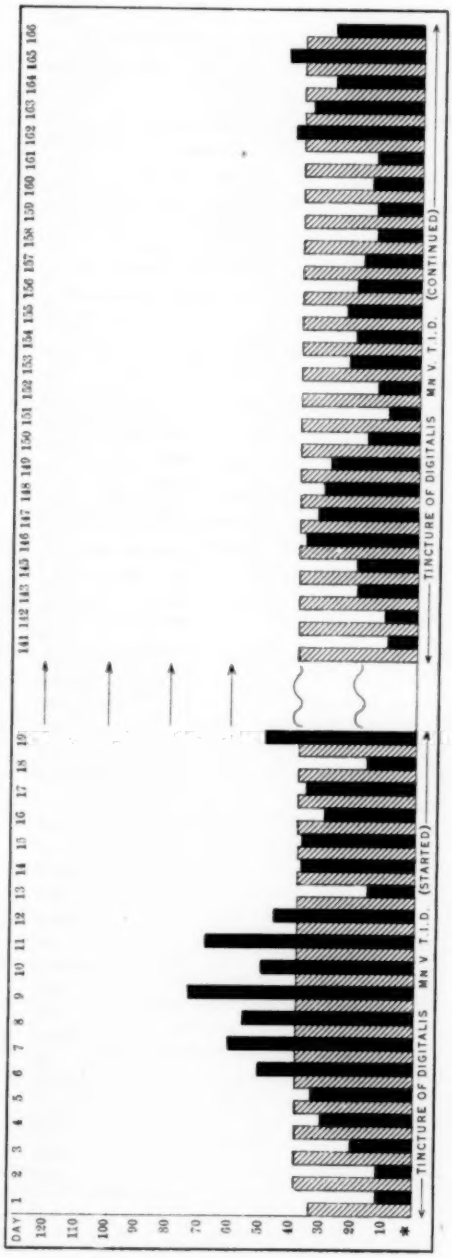
Two characteristic curves of water balance are presented for contrast.

Case Reports.—Case I (2807), a white school-boy, aged nineteen years, presented the picture of cardiac decompensation in cough, palpitation, extrasystolic arrhythmia, general anasarca, pulmonary congestion and hepatic engorgement. The occasion of his admission was this exacerbation of cardiac incompetency, which had originally dated back to his eleventh year when he had suffered from rheumatic fever. The heart showed double aortic and mitral lesions. With rest in bed, small doses of digitalis, fluid and salt restriction, an immediate and continued improvement was effected. The customary early positive water balance occurred (Chart II). An excellent output-intake ratio was maintained; and particular attention is directed to the wave like tendency of the output curve.

Case II (5203), a white male, aged fifty-three years, farmer and well driller by occupation, presented the clinical picture of cardiac decompensation dependent upon myocardial degeneration. Influenza complicated by pneumonia eight months prior to admission was the precipitating factor, whereas arteriosclerosis appeared to be the only etiologic background. An arrhythmia proved to depend upon auricular flutter and right bundle-branch block. Edema advanced slowly and jaundice deepened. The development of coupled beats from extrasystoles under digitalis therapy led to its discontinuance on the thirtieth day. Significantly there never occurred a positive water balance in this case nor was the 60 per cent plus output-intake ratio exceeded except on one day (Chart III). Death ensued on the fifty-third day.

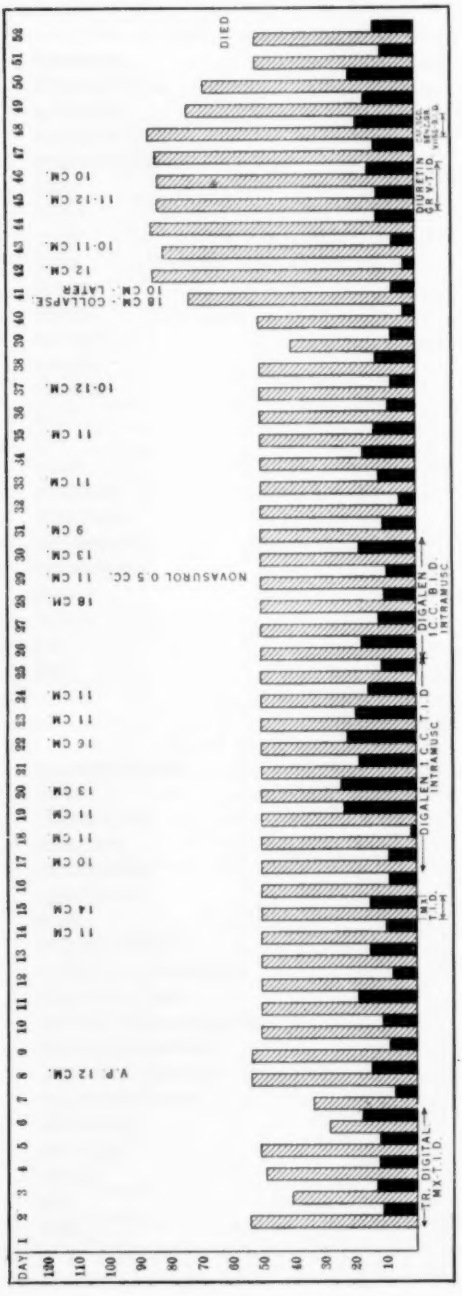
Factors Influencing Diuresis in Cardiac Decompensation. *Rest in Bed and Diet.* In conserving cardiac reserve and in exacting a minimum of myocardial energy, physical rest meets two primary indications for the treatment of decompensation. The French

CHART II.



* All volumes are given as fluid ounces; hatched columns represent intake; solid, output.

CHART III.


DAY
DIED
V.P. 12 CM.
14 CM
11 CM
10 CM
11 CM
11 CM
16 CM
11 CM
11 CM
18 CM
NOVASUROL 0.5 CC.
13 CM
9 CM
11 CM
11 CM
10-12 CM.
18 CM - COLLAPSE
10 CM - LATER
12 CM.
10-11 CM.
11-12 CM.
10 CM.
DIGITALIZE TID
DIGALEN
INTRAMUSC
TR. DIGITAL
MX T I D.

school has long supported the diagnostic difference in the nocturnal diuresis of cardiac and renal cases. In cases of cardiac decompensation, there occurs "a veritable dissociation in the elimination of the urinary water and chlorids," in that contrary to the nephritic the night urine is low in chlorids. (Vaquez[8]) Regardless of the factors concerned, diuresis with rest in bed is almost constant in the edematous cases of cardiac decompensation.

The importance of dietetic control in the management of the edema of decompensation has long been recognized. It has resolved itself into the restriction of the sodium chlorid and the water intake. Hippocrates[9] recommended the following course in the treatment of dropsy: "The patient should eat dry and acrid things, for thus will he pass the more water, and his strength be kept up." Various modifications of the Karell regimen constitute the accustomed procedure. In the Wisconsin General Hospital, unless there be special contraindications, the decompensated patient is given 1000 to 1500 cc. of fluid daily on admission. As other articles of diet are added, the salt-poor restriction is enforced until water logging disappears. No effort is made to separate the results of rest in bed and the dietary restrictions. Particular attention is directed to the early period of diuresis with rest in bed and appropriate diet in evaluating the effect of any concurrent type of treatment. The following case illustrates this point:

Case III (6075), a white male, aged forty-four years and a farmer by occupation, was first admitted on September 29, 1926, complaining of shortness of breath. Four years previously he had experienced an attack of precordial pain lasting a week; but evidences of circulatory incompetency first appeared with dyspnea and edema in 1923. Periodic exacerbations of the edema of the legs and scrotum have interfered with work from time to time. The only illness, other than the above mentioned, with a possible relation to the chief complaint, was influenza in 1918.

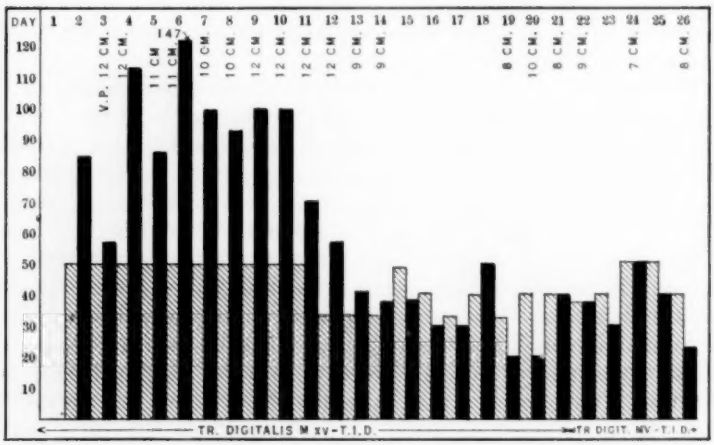
The physical examination established marked cyanosis, emphysematous type of chest, basal congestive râles, marked enlargement of the heart (particularly to the left), woodeny mitral first sound and accentuated pulmonic second sound, systolic blood pressure 134 mm., diastolic 60 mm., liver palpable and pulsating 8 cm. below the costal margin, spleen just palpable, marked edema of the legs and scrotum, positive centrifugal venous pulse. Laboratory examinations added nothing to the picture. No evidence could be gathered to substantiate the suspicion of an adherent pericardium.

A conclusion of cardiac decompensation depended upon myocardial degeneration was drawn. Significant were the evidences of tricuspid insufficiency. Under rest in bed, limitation of fluids (1500 cc.) and moderate doses of digitalis (℥xv, t. i. d.) there was quickly established a positive water balance (Chart IV) with coincident and progressive subsidence in the edema and other evidences of cardiac decompensation.

On two subsequent admissions, the same clinical situation pertained; but so dramatic had been the diuresis on the original observation that on both of these re-admissions the patient was simply put to bed on a salt-poor diet with a restriction of fluids to 1500 cc. Curves of diuresis comparable to that of the first admission were obtained in both instances

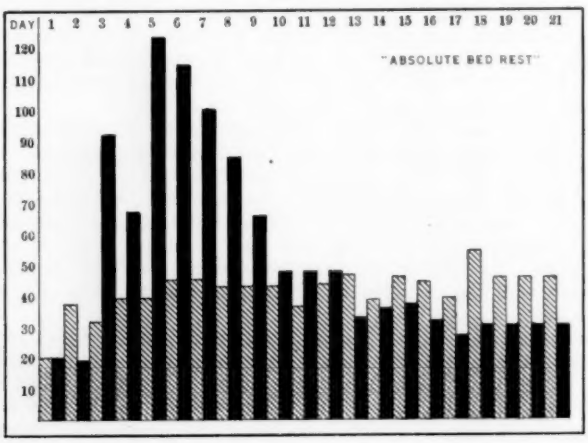
(Chart V); and interestingly in all periods of hospital stay a satisfactory ratio was maintained between output and intake succeeding the primary period of diuresis.

CHART IV.



Digitalis. This drug has occupied an unexcelled position in the treatment of dropsy since the original observations of Withering.[10] His injunctions relative to the physiologic limits of the drug indicate

CHART V.



his ideas as to the importance of its several actions. "Let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels." Interestingly he controlled purging by opium since

digitalis apparently had less diuretic action in the presence of diarrhea. A further point of Withering's practice with regard to the treatment of dropsy is interesting in another relation: "The patients should be enjoined to drink very freely during its operation. I mean, they should drink whatever they prefer, and in as great quantity as their appetite for drink demands. This direction is the more necessary as they are very generally prepossessed with an idea of drying up a dropsy by abstinence from liquids, and fear to add to the disease by indulging their inclination to drink." He outlined the limitations and the usefulness of the drug thus: "It seldom succeeds in men of great natural strength, of tense fiber, of warm skin, of florid complexion, or in those with a tight and cordy pulse. If the belly in ascites be tense, hard, and circumscribed, or the limbs in anasarca solid and resisting, we have but little to hope. On the contrary, if the pulse be feeble or intermitting, the countenance pale, the lips livid, the skin cold, the swollen belly soft and fluctuating, or the anasarcous limbs readily pitting under the pressure of the finger, we may expect the diuretic effects to follow in a kindly manner."

From a practical standpoint little can be added to Withering's observations, but his conclusions admit of a different explanation for the diuresis on the administration of digitalis in cardiac dropsy. Many clinical investigators (Mackenzie,[11] Cushny,[12] Cohn,[13] Christian[14] and others) have reported diuresis from digitalis only when there is edema. The present viewpoint in this matter is well expressed by Hatcher:[15] "None of the drugs of this group are actively diuretic through any direct action on the kidneys. They induce diuresis solely through an improved circulation. That does not mean either a higher or a lower blood pressure in every case: it means a more effective circulation, one better adapted to the needs of the individual patient. This sometimes means an increase, sometimes a decrease, in pressure." (Chart IX.)

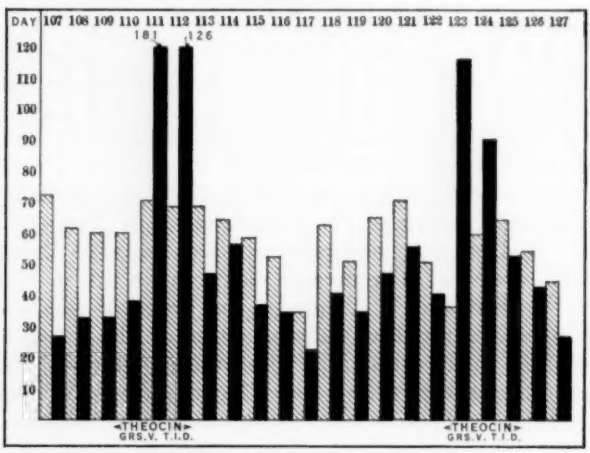
Xanthin Diuretics. Marvin[16] has very ably discussed this important group of diuretics, caffein, theobromin and theophyllin. His cases of congestive heart failure received the usual digitalis therapy, which was effective in the relief of edema in 36 of the 77 patients treated. Failing to effect diuresis with digitalis, the various xanthin diuretics were exhibited in turn. Theobromin proved more effective than theobromin sodiosalicylate, and theophyllin was the most active of the group.

The experience in the small group of cases under discussion strongly supports Marvin's conclusions; but no distinct contrast in the diuresis effected in the arteriosclerotic hypertensive myocardial cases as compared with the group of the rheumatic background could be deduced. Vertigo, headache, nausea, gastric distress and vomiting limit the wider usefulness of theophyllin. Theocin, the synthetic theophyllin, has repeatedly demonstrated

its diuretic potency after bedrest, dietary control and digitalis have failed to effect improvement.

CASE IV (3866), a white male, aged forty-three years, laboratory technician by occupation, was admitted for the second time in a state of grave cardiac decompensation, on June 15, 1927. The background for this condition was found in a hypertensive myocardial degeneration. Waterlogging was extreme and recurrent. The response to rest in bed, salt poor diet, fluid restriction, digitalis and venesection was erratic. The diuresis on the administration of the xanthin derivatives was prompt and repeated as may be gathered from Chart VI. The most striking incidence of this action occurred on the one hundred and fourth day, when on the exhibition of theocin (grains 10, three times daily) the patient excreted 10,055 cc. of urine with an intake of 2040 cc. The duration of hospitalization rules out rest in bed and dietary responsibility for the occurrence of diuresis.

CHART VI.



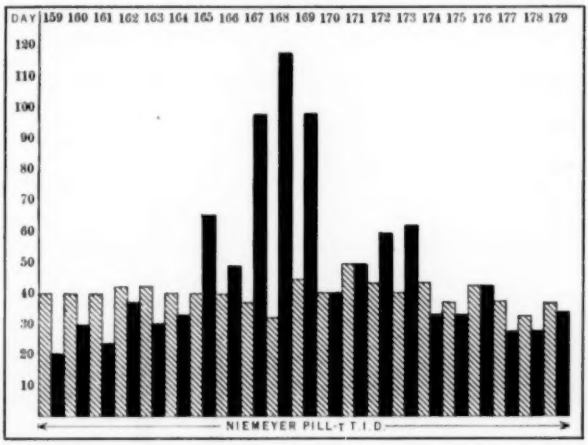
Mercury. This chemical operates as an irritant diuretic, and for this reason the integrity of the kidney should be ascertained before its exhibition. Furthermore, it is necessary that the mercury enter the circulation. For this reason, Massa hydrargyri of the Niemeyer pill has been replaced by calomel in our practice. With a compound of this order, it is difficult to evaluate the effective fraction; but if the digitalis alone has been ineffectual in combating the edema, the success of the combination (digitalis, squills and calomel) may be inferred to arise from the mercury. This reasoning is not above criticism, but such is the natural inference. Not infrequently the Niemeyer pill is successful, when digitalis or digitalis and the xanthin diuretics have been unavailing.

CASE V (6528), a white male, aged fifty-five years, had been a cardiac cripple for six years as the result of a rheumatic carditis. From the observa-

tions of this period of decompensation the conclusion of the following sequence of events was derived: rheumatic endocarditis involving the aortic and mitral valves, cardiac hypertrophy with myocardial degeneration, auricular fibrillation and relative tricuspid insufficiency, arteriosclerosis and hypertension.

Response to rest in bed, diet, fluid and salt restriction, paracentesis abdominis, digitalis and the xanthin diuretics was prompt and satisfactory. The accompanying segment of his complete chart (VII) was selected because

CHART VII.

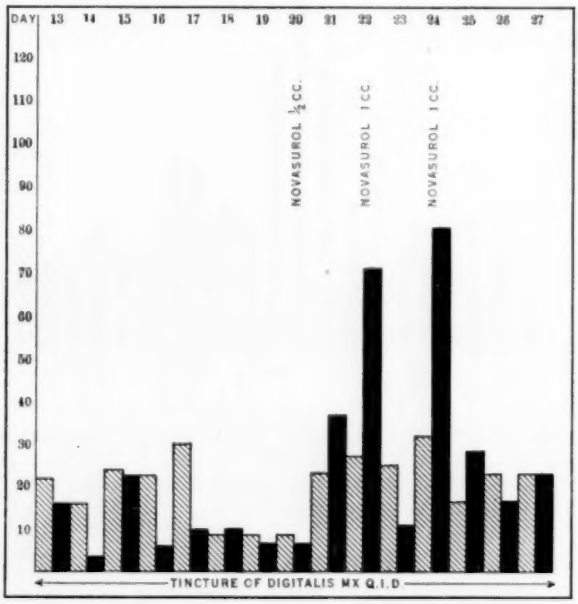


it demonstrates a period of diuresis at an interval of hospitalization (one hundred and fifty-nine days) of sufficient length of time to rule out the factors of rest in bed and diet and apparently dependent upon the administration of the modified Niemeyer's pill.

Of recent origin is novasurol, a mercurial adapted to intramuscular and intravenous use. Keith, Rowntree and others[17] were responsible for its general use in this country in cirrhosis of the liver and nephritis, particularly, while the application of its diuretic action in cardiac edema was advised by Crawford and McIntosh.[18] Their results ranked novasurol as a final court of therapeutic appeal, after digitalis had failed. Of its potency, there can be no reasonable question. Ptyalism, nausea, vomiting, diarrhea, albumin and red blood cells in the urine have been reported from novasurol. Both of 2 cases showing mild evidences of mercury poisoning after its use in the Wisconsin General Hospital had shown a phenolsulphonephthalein output of less than 50 per cent prior to its administration; and since it was the only evidence of renal insufficiency in either case this criterion has been used for the final judgment as to the wisdom of exhibiting novasurol. Case VI is an example of the action of novasurol on a very mild scale.

CASE VI (10303), a negress, aged fifty years, domestic by occupation, presented dyspnea, general anasarca, passive congestion of the lungs and liver, mitral valvulitis, cardiac hypertrophy and dilatation, hydrothorax and ascites. Rheumatic fever at twenty-four years of age had been the etiologic factor in the endocardial lesion, apparently. Arterial hypertension completed the picture. Rest in bed, venesection, theophyllin and digitalis effected some general improvement, but the fluid accumulations and edema persisted. The first sharp positive fluid balance was effected by the intramuscular administration of novasurol (0.5 cc.) on the twentieth day of hospitalization. Apparently in response to each of the three doses of this mercurial drug, diuresis occurred (Chart VIII.)

CHART VIII.



Interesting in the group under study has been the apparent delay in diuresis after novasurol, when the principal seat of the dropsy has been a serous cavity. In such cases a lag of twenty-four to thirty-six hours has been remarked in place of the accustomed prompt diuresis. No experience has been had with the coincident use of ammonium chlorid and novasurol.

The results of the study of the various drugs with relation to diuresis in these cases are enumerated in Table III.

The small numbers involved do not admit of generalization, but at a glance the advantage of theocin over theobromin sodiosalicylate and of novasurol over theocin would seem apparent. Niemeyer's pill obviously holds a relatively high position and is worthy of consideration. In evaluating the utility of digitalis, as with the

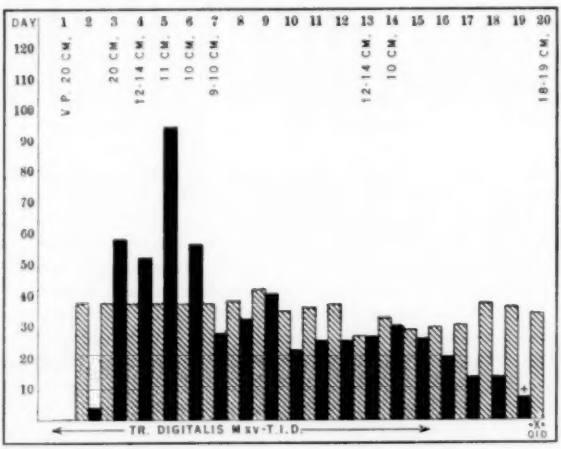
other drugs, no virtue is attributed to the rise in urinary output, apparently almost constant to cardiac decompensated cases with edema on bedrest and dietary control. If this circumstance be taken into consideration, the remarkable effect of digitalis in bringing about diuresis becomes apparent.

TABLE III.—RESPONSE TO DRUGS.

Drugs.	Administration.	Result. +	?	0
Theobromin sodiosalicylate	First	2	3	5
	Repeat	0	1	0
Theocin	First	4	2	4
	Repeat	2	1	1
Novasurol	First	7	1	5
	Repeat	7	0	0
Niemeyer pill	First	5	0	1
	Repeat	0	0	0
Digitalis	Alone	55	5	10
	Combined	10	0	1

Mechanical Factors. The relationship between the venous pressure and the urinary output has been previously mentioned. It can best be demonstrated by an illustrative case.

CHART IX.



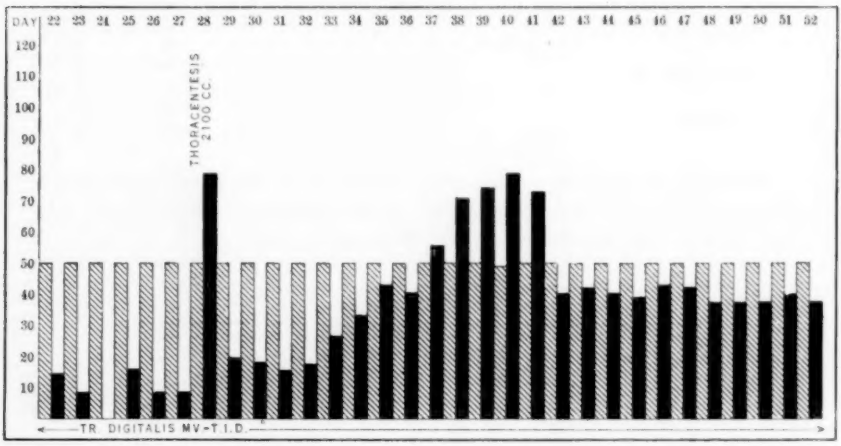
CASE VII (1976), a white female, aged sixty-two years, domestic by occupation, gave a history of scarlet fever and repeated attacks of tonsillitis, prior to tonsillectomy ten years ago. Evidences of cardiac incompetency, orthopnea, cough, precordial pain and abdominal distention, dated back six months. As a background for the decompensation there were determined a double mitral lesion, cardiac hypertrophy and dilatation with relative tricuspid insufficiency, and arteriosclerosis.

A fall in venous pressure was marked by a coincident diuresis (Chart IX). To emphasize the important interrelation of these factors a subsequent

rise in the venous pressure resulted in a sharp fall in the output. The influence of digitalis therapy in this relation may be clearly inferred from the time relationship of its exhibition and withdrawal to the improvement and the recrudescence in circulation incompetency.

Occasionally, striking changes in the water balance result from the removal of fluid accumulations from one or other of the serous cavities. Just how much of this effect is determined by the improvement in the general circulation is impossible to state. In any event Case VIII is an excellent example of the occurrence.

CHART X.



CASE VIII (3754), a white male, aged seventy years and a building inspector by occupation, was readmitted on May 25, 1926, complaining of progressive insomnia and dyspnea. The original findings of arteriosclerosis with myocardial degeneration, right bundle-branch block and cardiac decompensation were confirmed. From a mechanical standpoint, the existence of a bilateral hydrothorax was deemed highly important. Accordingly, the left thorax was aspirated on the eighth day and 1800 cc. of a straw-colored translucent fluid obtained. The subjective and the objective improvement after this procedure were not remarkable. Furthermore, an intolerance to digitalis led to the continuance of inadequate dosage. Singularly a markedly negative water balance pertained and from the time of admission until the second thoracentesis on the twenty-eighth day there occurred only two days of a 60 per cent plus output. The reaccumulation of fluid in the left chest led to the second aspiration and the curve of diuresis thereafter is most striking (Chart X). Concurrent general improvement attended the alteration in the water balance.

Multiple scarifications for the relief of tension in edema of the legs have been attended at times not only by marked loss of fluid by this route with general improvement but also by a subsequent diuresis.

Conclusions. 1. By reason of the circulatory relations of the kidneys, their functional activity is intimately bound up with the integrity of the general circulation. Hence, an unusual prognostic importance is attached to the study of the water balance in cardiac decompensation.

2. The simplicity of the output-intake observations should recommend their routine application to the general practitioner in the group of cases under discussion.

3. The influence of various physical and medicinal factors is discussed with reference to diuresis in decompensation. Calcium chlorid and ammonium chlorid have been used too infrequently to warrant their inclusion in the present relation.

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THE HEREDITARY TYPE OF ANGIONEUROTIC EDEMA.

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Quincke's disease, or angioneurotic edema, commands the interest of students of medicine because it belongs in the realm of the unknown and because of the hope that they may discover new and pertinent facts to aid in unveiling the mystery with which it is

surrounded. This disease is of special interest because of its protean symptomatology, the diversity of opinion regarding its etiology, and the fact that it may or may not have familial characteristics.

The familial type of the disease is the least common and because of its rarity we are adding to the literature the reports concerning another afflicted family.. The family consists of twenty-four members representing four generations. Six members of this family probably afflicted with the disease have died suddenly: two of undoubted edema of the glottis, two of obscure gastrointestinal colic, one of dropsy and one of heart disease. In this respect the family does not differ from the twenty-one others that have been described in the literature.

Report of Cases. CASE I.—A man, aged thirty-three years, registered at the clinic, March 9, 1923, complaining of cutaneous swelling and bowel trouble. For at least ten years he had been subject to attacks of localized edema of any area of the body, but especially the extremities, neck, lips, scrotum and throat. The attacks occurred about once a month, and he was incapacitated for two or three days. A typical attack was usually ushered in with tingling over a small area. Within a few hours the part became noticeably swollen; this progressed for from six to twelve hours, then gradually subsided for a like period. The swollen area was sharply defined with a definite ridge, probably about 1 cm. deep, which slowly spread "like a rising tide." Pain, itching or color change was not associated. The edema constituted a uniform tense nonpitting swelling. The involvement was usually unilateral, but had been bilateral and symmetric.

Four attacks had occurred, associated with marked edema of the face and neck, in which the patient became panicky, felt as though he was suffocating and breathed, talked and swallowed with difficulty. He felt best when lying down. The entire pharyngeal mucosa became swollen and the uvula was greatly enlarged, and hung down into the lower part of the pharynx.

For many years the patient had suffered periodically from bowel trouble, of which the dominant feature was colic. The distress began in the left iliac quadrant, gradually spreading over the entire abdomen, becoming progressively more severe. After a period of from twelve to fifteen hours he felt faint and weak, usually breaking out in profuse perspiration. On several occasions syncope developed. The abdomen was distended, but there was no flatulence. Usually the bowels did not move even with the aid of drastic cathartics. During the subsidence of an attack he noticed a great deal of borborygmus. He was unable to eat during such an attack; the tongue became heavily coated and the breath foul. These attacks may have been independent of or associated with the cutaneous edema. He usually noticed oliguria during an attack and polyuria afterward. There were no digestive disturbances in the interim and no vomiting during the crisis.

The patient's neuropathic tendencies were shown by excessive nervousness, worry or depression and aërophagia. He could not ascribe a definite cause to his attacks. They seemed sometimes to follow slight trauma and sometimes they occurred after he had partaken of tomatoes, strawberries or lemonade. Such food, however, had been taken repeatedly without the precipitation of an attack. He had never taken antitoxin or serum. He had never suffered from hay fever, asthma, toxic dermatitis or purpura or other hemorrhages.

The general examination was negative, except for the presence of inguinal hernia and rather marked myoidema and dermographia. While the patient was in the hospital for the repair of the hernia angioneurotic edema, involving the left arm to the elbow and the sole of the left foot, developed. The arm showed increased turgidity and the temperature of the affected area was 98° F. as compared to 94° F. for a corresponding area on the normal arm. The pulse rate was 60. The actual difference in circumferences of the affected and unaffected arms measured in centimeters was as follows: palm, left 24.5 and right 22; third finger, left 8 and right 7; wrist, left 19 and right 18; thumb, left 7 and right 7; forearm, left 27.5 and right 26; arm, left 31 and right 31.

The capillaries were studied and the volume of blood determined by Brown, both during and after the attack. Microscopic observations of the capillary loops during an attack, and three weeks afterward did not show change. The injection of vital red dye did not show increase in permeability nor was there extravasation. The results of determinations of blood volume made during an attack and again three weeks afterward are as follows:

	Weight, kg.	Height, inches.	Hematocrit, per cent.		Total plasma volume for each kilogram, cc.	Whole blood volume for each kilogram, cc.	Hemoglobin (Palmer), per cent.
			Plasma.	Erythrocytes.			
During attack	74	68.75	57	43	64	113	133
Three weeks afterward	70	....	60	40	57	94	111
Normal	..	....	60	40	50	90 to 100	

Skin sensitization tests for beef, tomato, strawberry, potato, lactalbumin, pork, whole wheat, horse serum, whole egg and oats, carried out with a control, were all negative. Tests of the blood showed urea, 22 mg.; urea nitrogen, 10.3 mg., and uric acid, 5 mg., for each 100 cc. A fragility test of the erythrocytes was 0.44 to 0.34 per cent as compared to a control 0.42 to 0.34 per cent. Prothrombin time ranged from ten minutes for 2 drops to fourteen minutes for 8 drops. Coagulation time by the Boggs method was five minutes and by the Lee method nine minutes. Calcium coagulation time was nine minutes and bleeding time two and five-tenths minutes. There were 192,000 platelets. The urine was normal. A complete blood count was normal. The Wassermann test (Kolmer modification) was negative. The basal metabolic rate was −1. Examination of the fundus and a roentgenogram of the colon were negative. Roentgenograms of the teeth showed questionable infection of three.

A recent letter from the patient stated that his general health since the operation for hernia had been good except for the attacks mentioned. He believes these are less severe than they were a few years ago. Months sometimes elapse without attacks, but they may occur as often as every two weeks. There had been only one laryngeal attack in the last five years, but numerous surface swellings and gastrointestinal attacks have occurred (Fig. 1).

Family History. The disease was probably inherited from the father's side of the family. The paternal grandmother and the great grandparents on her side apparently died of old age. The paternal grandfather dropped dead suddenly, presumably from heart disease. Nothing is known of the great grandparents on the paternal grandfather's side of the family. The family has been traced for five years.

The patient's father, now aged sixty-seven, stated that for many years swellings, especially of the hands and scrotum, had occurred, and that for a similar period gastrointestinal attacks had been frequent. He described such attacks as beginning with distress high in the epigastrium, and growing more and more severe as it traveled downward; by the time it had reached the lower part of the abdomen it became severely acute. The pain persisted until the bowels moved, then gradually subsided. He sometimes became quite ill and vomited during the attack. Sometimes certain foods seemed to be the cause and again he seemed unaffected by the same foods.

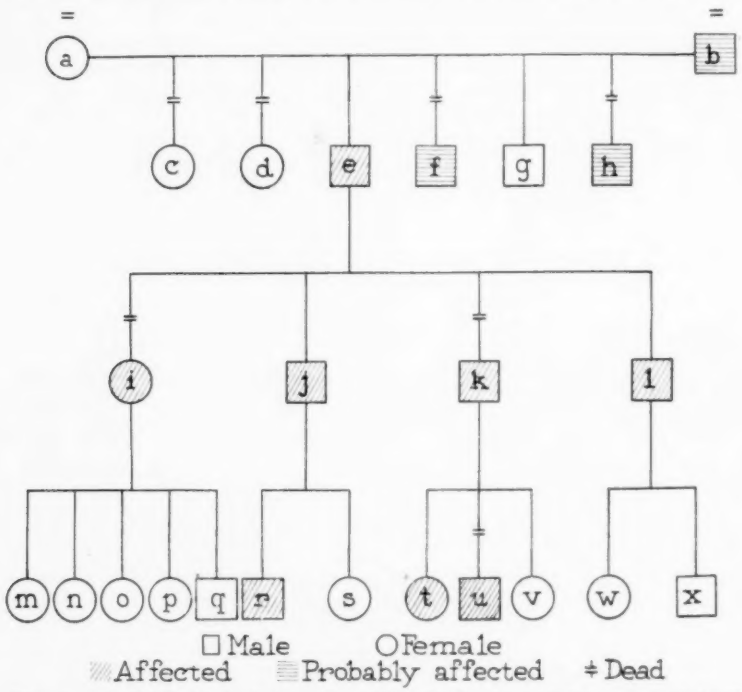

FIG. 1.—(*a*) Died, aged ninety; (*b*) sudden death; (*c*) and (*d*) causes of death unknown; (*e*) patient's father aged sixty-seven, cutaneous and gastrointestinal type; (*f*) sudden death, aged fifty-eight, gastrointestinal colics; (*h*) sudden death as youth, "dropsy;" (*i*) died of edema of glottis, aged thirty-five had cutaneous, gastrointestinal and laryngeal type; (*j*) aged forty-two, gastrointestinal and cutaneous type; (*k*) died aged twenty-seven, edema of glottis also had cutaneous and laryngeal type; (*l*) patient aged thirty-seven, cutaneous, gastrointestinal and laryngeal type; (*r*) aged nine, cutaneous type; (*t*) aged sixteen, cutaneous and laryngeal type; (*u*) died aged fourteen, suddenly obscure gastrointestinal colic (*g*, *m*, *n*, *o*, *p*, *s*, *v*, *w*, *x*) living and healthy.

Two aunts had died of unknown cause. One uncle had suffered from gastrointestinal attacks for years and died suddenly at the age of fifty-eight years. One uncle died suddenly of "dropsy" when a young man. One sister, from the age of twenty years, had had repeated attacks of edema of the larynx and died in such an attack at the age of thirty-five years. In her youth repeated attacks of swelling of the hands, feet and neck, and bowel trouble similar to that described by the patient, had occurred. This sister had five children, all living and well. The oldest is only nineteen years of age, however, and the malady may yet develop.

One brother had had repeated acute gastrointestinal attacks of unknown cause since the age of twenty years. At first they occurred every two or three weeks, lasting about two days, but for the last six years only three had occurred each year. During an attack there was severe abdominal pain, bloating, soreness and a feeling of obstruction. Nausea, profuse perspiration, faintness and scotoma were frequent symptoms. During such an attack little if any urine was passed. Cutaneous swellings, usually of the genitalia or arms also occurred. This brother had two children; the oldest, aged nine years, had suffered from swellings of the body and from laryngeal attacks; one of the worst attacks had occurred during chickenpox.

One brother died at the age of twenty-seven years, during his first attack of edema of the larynx. This followed the administration of serum given as a therapeutic measure in the treatment of transient swelling of the surface of the body, that had recurred for many years. This brother had three children, all aged less than sixteen years. The oldest, a girl, had suffered repeatedly from swelling of the surface of the body and attacks of edema of the larynx; in one such attack she almost died. The second oldest child, aged twelve years, died suddenly in March, 1926. The diagnosis was appendicitis; operation was not performed. Abdominal seizures had occurred previously but surface swellings had not been noted.

The following 3 cases of angioneurotic edema or urticaria, although not of the familial type are reported because of the diversity of symptoms and the special studies which were carried out on blood volume and the type of capillaries.

Case II.—A Greek, aged thirty years, registered at the Mayo Clinic, April 13, 1923. Prior to the onset of urticaria he had been in perfect health, except for occasional attacks of migraine. Early in 1917, within ten minutes after having eaten buckwheat cakes, diffuse, white, itching swellings appeared over the entire body. The face was so bloated that the features were unrecognizable. For half an hour he was so dyspneic; he could scarcely breathe or talk. The abdomen became distended and he vomited; there was no colic. Since then when he is in a room where buckwheat flour is being mixed, if he eats buckwheat cakes or any kind of nuts, or if he is bitten by a mosquito, a severe reaction, characterized by itching wheals over the body, greatly swollen lips, marked dyspnea, profuse nasal secretion, sneezing and blockage of the nose develop immediately. This passes off in from thirty to forty-five minutes. Hay fever, asthma or purpura has not occurred.

The patient was in good physical condition. The systolic blood pressure was 130 and the diastolic 78. The urine and blood were normal. The Wassermann test of blood and spinal fluid and the gold-sol curve were negative. Examination of the nose and throat disclosed septic tonsils and deflection of the nasal septum with obstruction. A roentgenogram of the chest was negative.

Skin-sensitization tests for whole egg, oats, lactalbumin, peanuts and corn, carried out with a control, were all negative. The tests for English walnuts and potatoes were graded 1+, and for buckwheat and whole wheat 3+. A study of the blood volume showed:

	Weight, kg.	Hematocrit, per cent.		Total plasma volume for each kilogram, cc.	Whole blood volume for each kilogram, cc.	Hemoglobin (Palmer), per cent.
		Plasma.	Erythrocytes.			
Patient	64	54	44	40	87	128
Normal	..	60	40	50	90 to 100	...

When the patient was last heard from, April 4, 1924, he was having attacks when he ate the food mentioned.

CASE III.—A man, aged fifty-six years, registered at the Mayo Clinic, March 26, 1923, complaining of hives, which had begun twenty years previously with "spells of locking of the stomach." There were severe attacks of constant cramplike pain in the epigastrium lasting three or four hours, leaving him none the worse, except for residual soreness which lasted three or four days. Nausea, vomiting, flatulence or fever had not occurred, and bowel movements were normal. The spells continued for ten years, occurring irregularly, perhaps once a week or skipping months at a time.

The attacks always began suddenly and stopped just as suddenly, so that he "could feel his stomach open up." Cutaneous swellings then occurred at intervals of from two to three days to weeks. Intense pruritus of the palms and the soles developed suddenly, and was followed by generalized eruption or wheals over the body, worse on the face. This would last for half an hour and as suddenly disappear. Two years previously attacks of tingling under the angle of the jaws occurred with a sense of fullness in the neck lasting a few minutes. Then profuse mucous nasal discharge and cough developed. The patient became dyspneic and coughed a good deal; the face became cyanotic and he felt as though he were dying. The attack passed off in about half an hour. Such attacks came irregularly, every few days or with an interval of weeks. The patient ate heavily, and believed that at times acid foods and too much water precipitated attacks. He also attributed the attacks to apples, cherries, onions, peaches and whisky. He was not susceptible to cold and had never had asthma or hay fever.

General examination disclosed obesity pulmonary emphysema, thyroid enlargement and cardiac hypertrophy, with evidence of myocardial degeneration and beginning decompensation. The systolic blood pressure on two occasions was 160 and 184 and diastolic 100 and 104.

A complete blood count, examination of urine, blood Wassermann test, gastric analysis and gastric roentgenograms were reported negative. A roentgenogram of the chest showed cardiac enlargement (graded 3), with congestion at both bases. An electrocardiogram gave a rate of 90, notched *P* wave in Leads I and II, left ventricular preponderance and inverted *T* wave in Lead I. A skin-sensitization test, carried out with a control, was reported as negative to grapefruit, whole egg, tomato, lactalbumin, beef, whole wheat, pork, casein, corn, rice, oats and potato. The capillaries were normal. A study of blood volume showed:

Weight, kg.	Hematocrit, per cent.		Total plasma, volume, for each kilogram, cc.	Whole blood volume, for each kilogram, cc.	Hemoglobin (Palmer), per cent.
	Plasma.	Erythrocytes.			
103	53	47	38	71	129

The patient, who is now sixty-two years of age, states that he is working every day, but continues to have the attacks, although less often than at the time of his examination.

CASE IV.—A man, aged thirty-four years, registered at the Clinic, August 22, 1923. In the spring of 1919 he had noted for the first time several isolated swollen areas on his scalp which soon disappeared. He was free from them until the fall of 1921, when several similar areas appeared on his

scalp during the course of the evening and were gone by the next morning. From this time on every two or three days, usually about 8 P.M., the feet, face, eyelids, hands, tongue, lips, buttocks or genitals became swollen, but the swelling had always disappeared by morning. Such lesions were sometimes single and sometimes multiple. They seemed particularly to follow slight trauma, such as swellings of the hands after he had driven a long distance, or of the feet after walking, or buttocks after he had been sitting for a long time. Twice during this period he had had laryngeal attacks with severe dyspnea and cyanosis. There was no gastrointestinal colic.

The general examination was negative. The systolic blood pressure was 130 and the diastolic 80. A complete blood count, analysis of urine, Wassermann test on the blood, roentgenogram of the chest, examination of the fundus and renal functional tests were all reported negative. The platelets numbered 276,000. Coagulation time (Lee method) was five minutes. The prothrombin time varied from thirteen minutes for 2 drops to twenty-five minutes for 8 drops. W. W. Duke* had made a thorough study for allergy and had reported that all tests were negative.

Definition. The term angioneurotic edema implies a condition characterized by acute massive ephemeral swellings of the skin, of various mucous membranes, or of the viscera; a swelling which recedes without leaving a residue. There is a strong tendency to recurrence, particularly in a previously involved area, and in certain cases with extraordinary precision of time. The duration of a single attack varies from hours to one or two days. The condition is chronic, extending over a period of many years apparently without ill effects; in fact, persons affected are usually free of organic disease.

History. Angioneurotic edema as such was first described by Strübing in 1885. Three years previously Quincke had reported the same syndrome under title of acute circumscribed edema. In his description he included not only the recurring edema, involving the skin and subcutaneous tissue, but also the recurring edema of the pharynx, larynx and gastrointestinal tract, as well as the intermittent serous effusions of joints. As far back as 1827 this condition was mentioned in the literature although not as an entity. In 1874 Cuntz reported 4 cases of recurring edema recognized as of angioneurotic origin. Henoch in the same year reported 4 cases of his own and 3 which he had noted in the literature of an unusual form of purpura of nervous origin which he classified as an entity characterized by recurring attacks of purpura, cutaneous edema, gastrointestinal crises and melena. Since Quincke's time various manifestations of this strange malady have been reported under many titles. Cassirer in 1901 reviewed 160 cases from the literature under title of acute circumscribed edema.

Literature. Angioneurotic edema and urticaria were regarded as one and the same prior to the time of Quincke: Oppenheimer still maintains their identity. Crocker regards angioneurotic edema as

* Personal communication.

giant urticaria. Stelwagon and Oppenheim distinguish the two conditions, but recognize their similarity. Kohn believes that urticaria involves the corium while angioneurotic edema involves the subcutaneous tissues. Halsted and Packard include angioneurotic edema, urticaria, asthma and hay fever in one group. Packard reported 36 cases of the occurrence of asthma and urticaria in the same or alternating attacks. Osler, in his third contribution on the subject, pointed out the relationship existent in simple erythema, erythema exudativum, erythema nodosum, herpes iris, certain of the purpuras (including Henoch's purpura) urticaria and angioneurotic edema. He concluded that they belong to one family in that they occur under similar conditions, that frequently the lesions may be substituted one for the other at different times in the same patient, that they tend to recur for many years, and that they cause identical visceral manifestations. Yarian, Chittenden, and Schlesinger concur in Osler's view and report cases in which such complications exist. Joseph and Cassirer reported the occurrence of hemoglobinuria associated with each recurring attack of angioneurotic edema. Packard reported a case of hematuria relieved by outbreaks of urticaria, Holmes one of acute local edema complicated by salivation and purpura, Küssner one of apparently causeless hemorrhages from mucous membranes simultaneously with edema, and Chittenden one of urticaria associated with gastrointestinal attacks of hematemesis or melena. Stokes has called attention to the relationship of erythema nodosum purpura and tuberculosis. Rosenow reported the relationship of erythema nodosum to nontuberculous infections. One of us (Lemon) reported the existence of eczema, adenoids and asthma in the same patient, and similar conditions singly or combined in two other children of the same family; one child of the family was not affected.

Etiology. The causes assigned to angioneurotic edema are almost as diverse as are the titles. It has been fairly well established that thermal changes bear a direct relationship, but whether as a primary or a precipitating cause has not been determined. Particular attention has been directed to its relationship to cold. Starr, Oppenheim, Widowitz, Wills and Cooper, Schlesinger, Cassirer and Morse have cited cases bearing out this view. Kohn, on the other hand, cited a case in which an attack was precipitated every time the patient placed her hands in hot water. Collins stated that attacks are more frequent in the summer and winter than in the spring and fall, due to the variation of surface temperature during and following exertion.

Anaphylaxis as an etiologic factor has frequently been observed. Nifong, Morse, Halsted and others have called attention to the relationship of the administration of diphtheria antitoxin to the occurrence of angioneurotic edema and urticaria. Lederman reported a case in which an attack developed as a result of contact

with a jelly-fish. Crowder and Crowder believe a streptococcic infection may result in an anaphylactic reaction. Halsted believes that toxin and autotoxin, probably of gastrointestinal origin, is a possible cause. Osler cited the relationship of certain foods, hydatids and shellfish to attacks in some cases. Infections have been considered as the causative factor. Matas quoted a case resulting from malarial infection in which cure was effected by quinin. Osler also showed the relationship of malaria and cholecystitis to certain cases. Oppenheimer and Joseph reported cases showing a direct relationship to the ingestion of alcohol. Miller and Pepper, in a study of the chemical condition of the blood, found retention of chlorids and nitrogen preceding and during an attack.

TABLE I.—TABULATION OF CASES FROM LITERATURE.

	Generations.	Members.	Members affected.	Deaths.	Remarks.
Osler	6	42	24	2	
Crowder and Crowder	5	64	28	15	
Ricochon	4	..	9	3	
Schlesinger	4	15	5	..	
Ensor	5	80	33	12	
Dinkelacker	2	4	3	..	Third member reported by Valentin.
Strübing	2	4	3	..	Father, son, daughter.
Falcone	3	..	2	..	Grandfather and child.
Krieger	2	..	2*	..	Mother and son.
Fritz	3	9	8	5	Deaths from edema of the glottis.
Roy	2	..	2	..	Mother and daughter.
Yarian	2	15	10	2	One died of edema of the glottis.
Griffith	2	..	2	2	Father and patient died of edema of glottis.
Harbitz	3	..	6	..	
Morris	2	..	3	1	Death from edema of the glottis.
Halsted	3	..	7	..	
Halsted	2	..	4	..	
Halsted	2	..	3	..	
Smith	2	..	2	..	Mother and daughter.
Mendel	4	12	9	6	Deaths from edema of the glottis.
d'Appert and Delille	3	..	5	..	
Dunlap and Lemon	4	23	11	6	Two died of edema of the glottis.

The relationship of angioneurotic edema to nervous disorders, either organic or functional has long been noted. It has been found in association with such nervous disorders as chorea, sciatica, hysteria, migraine, myasthenia gravis, epilepsy, cord tumor, neurasthenia and tabes. Simon reported a case associated with epilepsy. Börner, Joseph, Schlesinger and Cassirer have cited instances of its occurrence in association with exophthalmic goiter. We have frequently noted the occurrence of urticaria in cases of exophthalmic goiter and its alleviation by thyroidectomy. Collins does not believe that the edema associated with organic nervous disorders is the same as that associated with angioneurotic edema. He rather favors a neuropathic cause for the latter. Oppenheim, Quincke, Schlesinger, Widowitz, Cassirer, Bauke, Wills and Cooper, Kohn and Hallock state that it usually occurs in a neuropathic person, or in

a member of a neuropathic family. The relationship of psychic disturbances and especially of emotional instability has been emphasized by Strübing, Cassirer, Schlesinger, Ensor, Packard, Oppenheimer and Crowder and Crowder. The relationship of menstruation and the climacteric to its occurrence has been stated by Börner and Schlesinger. Börner reported a patient having attacks definitely occurring during menstruation and relieved by the onset of the climacteric. Quincke, Strübing and Collins believe that it is a form of vasomotor neurosis. Crowder and Crowder agree with the latter view, but believe that it is dependent on a capillary irritant. The latter, according to Crowder and Crowder, causes either increased secretion of lymph or causes the walls of the vessels to become more permeable, allowing increased transudation. It is Crocker's belief that the whole process is a vasomotor disturbance with spasm of the wall of the vessel followed by paralytic dilatation and stasis or retardation of the circulation in the papillary layer of the skin.

Trauma, even though slight, such as irritation to the genitalia in bicycling may be an etiologic factor. Halsted noted edema of buccal and laryngeal mucous membranes following the use of throat sprays and of applications of zinc chlorid. Three of Crowder's patients died of edema of the larynx after extraction of teeth. Briggs reported 4 cases of fulminating pelvic edema resulting from a nidus of tubal inflammation.

Etiologic Influence of Heredity. It has been recognized since Quincke's observations that in certain of these cases there is a distinct hereditary tendency. It was not until Osler's report, however, that general attention was attracted to the hereditary tendency. Crowder and Crowder believe that direct descent of the tendency is so constant as to suggest inheritance in the strict sense of a trait transmitted as a dominant characteristic under the Mendelian law. Ensor stated that members of an affected family who escape are less likely to transmit the disease than are those affected. Crowder and Crowder did not observe an instance of it in a descendant of an unaffected parent and only twice did all the children of an affected parent escape. The line of inheritance was always direct, not skipping and reappearing. In only 1 instance did Ensor find the offspring of an unaffected parent affected by the disease and in this case there were 7 other children free from the disease. In the family reported by Osler there was 1 unaffected parent who had 3 children all affected, but in the remainder of the family the transmission was always direct. Also, in the families reported by Schlesinger and Ricochon there was no instance of skipping and reappearing. In the family discussed here the transmission was direct through four generations.

The question has been raised repeatedly as to whether inheritance is through the paternal or the maternal side of the family. Fairbanks believes that it is transmitted only through the maternal line

in the acute form. Yarian's cases show preponderant transmission through the maternal side. Cassirer records an instance in which inheritance was entirely through the male. The cases of Quincke, Dinkelacker, Valentin and Strübing were transmitted from father to son. The families reported by Osler and Ensor showed repeated transmission through the male. The families reported by Ensor showed inheritance through the male line in 6 instances for four generations and in 2 instances for five generations. The reports of Osler, Schlesinger, Crowder and Crowder, Ricochon and our case each showed 1 instance of transmission through the male for four generations. Crowder and Crowder also reported an instance of transmission through the female for as many as three generations.

According to Fairbanks, the mortality in the hereditary cases is about 16 per cent, and in the remaining 84 per cent about 6 per cent of patients are in imminent danger during some attack. The cause of death was edema of the glottis in most cases, and usually in adult life. Osler reported 7 deaths in 29 cases (24.1 per cent), but included erythemas, purpuras, and so forth. Ensor reported 12 deaths from edema of the glottis in 35 cases (35 per cent), Crowder and Crowder 15 deaths in 28 cases (51.5 per cent), Yarian 3 deaths in 9 cases (33 per cent), and Fritz 5 deaths in 8 cases from edema of the glottis. Griffith reported 2 cases and Morris 1 from edema of the glottis. McDowell reported an incidence of 30 deaths (37 per cent) among 110 familial cases reviewed by him. In the family reported here there have been 6 deaths, 2 of which were from edema of the glottis. Four deaths were sudden and occurred in questionably affected members of the family (tabulation.)

Symptoms and Course of Disease. Ensor has divided the cases into four clinical groups: (1) in which subcutaneous tissue alone is involved; (2) in which the mucosa of the respiratory and intestinal systems are primarily involved; (3) in which a combined form of edema begins in the face and spreads to the mucosa of the pharynx and larynx, and (4) in which intestinal colic exists without external signs of edema. According to Ensor, Groups 1 and 4 constitute the most common type and are the least dangerous.

Group 1. The cases in this group are the most common. The lesion is typically a large, pale, cool swelling not accompanied by itching, developing rapidly, persisting indefinitely, then subsiding without leaving evidence of its existence. It does not pit except perhaps during recession. The lesions vary greatly in size in various attacks and in different persons. The onset is usually preceded by a short period of intense itching.

Groups 2 *and* 3. This type of angioneurotic edema is much more common than is generally believed. As stated by Ensor, it may start in the larynx itself or it may spread to the larynx from the face or buccal cavity. The former is far more serious and accounts for most of the deaths in this group. The onset is sudden with

intense dyspnea, and suffocation and death soon ensue unless relieved within a few minutes. Griffith viewed the involved areas several times with a laryngeal mirror. The lesions appeared to be rounded, pale, jellylike, tense masses obscuring the cords. Both Morris and Griffith reported on the laryngeal lesion of a patient who died during an attack of edema of the glottis. The mucous membrane was very edematous, the edema extending down into the deeper connective tissue and muscle; even the tissues over the true cords were markedly affected.

The edema at the same time or independently may involve the nasal mucosa, the sinuses, pharynx, tongue, bronchial mucosa and lungs, accounting for the relationship noticed by Halsted and Packard in cases of angioneurotic edema, urticaria, asthma and hay fever. Ensor reported an instance of acute pulmonary edema. Bloodgood has reported on edema of the sinuses.

Group 4. Gastrointestinal attacks are second only in frequency to surface swellings. They may accompany, alternate with, or precede for many years the cutaneous manifestations. Bogart quotes Osler saying that gastrointestinal attacks occur in 34 per cent of all cases. In Osler's own series of cases 25 of 29 patients suffered from gastrointestinal symptoms. He believed that they did not cause death.

Morris reported noninflammatory edema of a piece of gastric mucosa recovered by lavage during an attack. Bogart reported a case in which he found blood-stained fluid in the peritoneal cavity on exploration, as is found in ileus, with edema of the ileum and jejunum obliterating the lumen of the bowel.

Bogart stated that such crises usually occur in men aged thirty to forty-five years. Colic is the predominant symptom and for years may be the sole manifestation, as in Cases 17 and 27 of Osler's series. The pain is sudden at the onset and severe. Bogart stated that the pain is in the midabdomen, and more or less continuous with paroxysms of greater severity. The patient may appear very ill and on the verge of collapse. There is little if any fever. The abdominal walls are tense, but not rigid, and there is no tenderness. Nausea and severe repeated vomiting are usually associated. The abdomen is distended and the bowels cannot be moved. Occasionally, however, diarrhea, meteorism and melena occur.

Bogart and Osler call attention to the similarity of these cases to those of gall stone or renal colic, intestinal obstruction from intussusception, perforated gastric or duodenal ulcer, appendicitis, hydronephrosis, tabetic crises and abdominal migraine. Osler reported 3 cases from the literature and 1 of his own of colic and melena leading to a false diagnosis of intussusception. In cases of children with colic he emphasized the necessity of taking a careful history of previous attacks of colic, of lesions of the skin or arthritis and of looking for purpura, erythema or angioneurotic edema.

Other organs and tissues have been less often involved. Osler reported endocarditis as a rare complication, usually in cases with intense arthritic purpura. He noted 14 cases of acute nephritis in which 5 patients died of uremia. He did not observe the condition in an uncomplicated case of angioneurotic edema. Oliguria was noted by Quincke and Schlesinger as well as ourselves. Schlesinger states that we cannot be sure whether the oliguria is due to edema of the kidneys or is on a circulatory basis due to vasomotor instability. Osler also reported arthritis or arthritic pain in 17 cases. Crowder and Crowder reported enlargement of the uterus in a girl aged eighteen years; the uterus increased to about the size of a "twenty-pound cannon ball" in thirty minutes. Talley noted involvement of the salivary glands and Küssner and Quincke noted ascites.

Oppenheim states that it is uncertain whether angioneurotic edema can cause brain symptoms. He has seen apoplectic attacks occur in a chronic variety of this malady which he felt was possibly of vasomotor origin. In Osler's Case 15 attacks of aphasia and hemiplegia developed, associated with the lesions of the skin.

Summary. The voluminous literature on angioneurotic edema has been briefly reviewed and the disease discussed in its relationship to heredity, etiology, and symptoms. Reports of cases of families described in the literature, have been tabulated. One family is added to those already described. It has not been possible to add much to the understanding of this strange malady.

In this report we have also included 3 cases that did not exhibit familial characteristics. They were added, however, because of the bizarre symptoms and because the studies of the capillary loops and blood volume might throw some light on the mechanism of the production of the edema. The same studies were made on the representative of the familial group, but they did not disclose variations either from those of normal persons or from those on cases without familial tendency.

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IPSOLATERAL EDEMA AND CONTRALATERAL JAUNDICE ASSOCIATED WITH HEMIPLEGIA AND CARDIAC DECOMPENSATION.

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Bizarre distribution of edema and jaundice is a phenomenon of more than passing interest to the theory of permeability. But few clinical examples, however, have been reported in the literature. It is for this reason that the following cases are presented and discussed from the point of view of their bearing on this important mechanism.

Case Reports. Case I.—Barney K. (No. 67864) was first seen at the age of ten years, suffering from chorea and mitral insufficiency. Twelve years later he developed a sudden right-sided hemiplegia presumably as the result of dislodgement of a clot from the auricular appendage. At this time his clinical picture was that of a classical case of mitral stenosis and insufficiency, auricular fibrillation and cardiac hypertrophy. About four months were required for convalescence from the hemiplegia. Three

months after this he became decompensated and had bronchopneumonia, but with rest in bed and digitalis his recovery was satisfactory. It should be noted that the liver was felt 3 cm. below the costal margin, whereas there was no peripheral edema. One month later however, he again became decompensated and again using the same régime recovered fair health. There was little of unusual note during these periods.

However, six months later he entered the hospital complaining of pain and swelling in his right hand, arm and leg. His heart was fibrillating and markedly insufficient, many râles were heard in the bases of his lungs and the liver was enlarged 6 cm. below the costal margin. The peculiar feature presenting itself was that in spite of some atrophy of the two right extremities, resulting from the old hemiplegia which had been previously noted, these limbs were very edematous. To our surprise no edema was found in the *left* leg, arm or over the sacrum. On the right side the deep reflexes were all increased over the left, but no positive Babinski or Oppenheim sign nor ankle clonus was found on either side.

The blood pressure was 118 systolic and 80 diastolic, and did not vary greatly throughout his course. After a few days in bed he became slowly jaundiced. The jaundice appeared only on the left side, the edematous parts of the residual hemiplegic side remaining clear. He became progressively more decompensated. Cyanosis appeared but much more prominently in the nails and the lobe of the ear on the edematous right side. As decompensation advanced, bilateral peripheral edema appeared. The patient died shortly thereafter.

On his last admission, the red blood cells numbered 4,200,000 with 87 per cent hemoglobin (corrected to oxygen standard); white blood cells, 15,000, with 80 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes and 3 per cent endotheliocytes. The stool showed no bile; urine bile ++++; blood urea, 0.26 gm. per liter. Icteric index = 50. Van den Bergh test gave a direct immediate reaction and the indirect = 9.4 units bilirubin (4.7 mg.) per 100 cc. of serum. Electrocardiographic records and Roentgen ray confirmed the diagnosis of rheumatic endocarditis.

Necropsy showed extreme calcification and distortion of the mitral valve. Many thrombi in the auricular appendages, infarcts of the lung and spleen, rheumatic aortitis, rheumatic auriculitis, and other changes characteristic of rheumatic heart disease were present. A terminal bronchopneumonia was also demonstrated. Cardiac cirrhosis was present to a marked degree in the liver, for example, reticulum-cell condensation as the result of long-continued chronic passive congestion.

Case II.—No. 71123 (female, aged thirty-seven years). Three years before admission to the hospital, this patient had a curettement, following which she suddenly became paralyzed in the right hand and arm. A few months after this she developed acute polyarticular rheumatism associated with endocarditis. Six months later she had the physical signs of typical rheumatic heart disease and her heart was fibrillating. Shortly thereafter began a series of convulsive seizures and transient paralyses, which strongly suggested multiple cerebral emboli. Three weeks before admission to the hospital, she became rapidly decompensated. Her legs and abdominal wall were massively edematous. The arm in which the paralysis had occurred became tense with edema even up to the neck but the other arm (left) remained free. Shortly before death she became slightly jaundiced but none appeared in the edematous arm and legs whereas the rest of the body showed an icteroid tint. The serum bilirubin was 3.75 mg. per 100 cc. serum; the blood urea, 1.04 gm. per liter.

Discussion. There is not at present any unqualified proof of the direct control of permeability by the nervous system. There are

many experiments and examples which suggest this however. If, for instance, the right cervical sympathetic system is removed from an animal, and fluorescein injected into the peritoneum, the dye may subsequently be seen in the right vitreous but none in the vitreous of the left eye.[1] Various secretions, such as the saliva, seem to be liberated as the result of permeability changes mediated by a nervous impulse.

Hemiplegia certainly produces vasomotor paralysis or instability. This is shown by the trophic changes in the right limbs and the ipsolateral cyanosis observed in our case.

A paralytic dilatation of the capillaries, resulting from the lack of tonic influence of the vasomotor system, may result in active transudation of fluid. From the work of Landis,[2] we may assume that the dilatation *per se* is not responsible for this occurrence, but rather must refer it to a change in cell permeability. A further factor resulting from vasomotor paralysis is arterial hyperemia. Increased filtration pressure is thus produced which in turn may facilitate fluid transfer from vessel to tissue. At present, there are not sufficient data to prove that there is a change in the osmotic pressure of the blood in these cases of regional edema.

Local anoxemia as a result of: (1) Deficient oxygenization of the blood in the lungs, and (2) increased oxygen consumption resulting from the stagnation of the blood in the capillaries may well be one of the causative agents initiating these permeability changes.

It is worthy of note that this patient had visceral manifestations of edema before any peripheral signs appeared and that when the peripheral signs did appear they were localized to one side. This raises the question of where edema first manifests itself in cardiac decompensation. If cardiac edemas are associated with capillary anoxemia we should anticipate that edema would first appear in the viscera and the peripheral signs follow later.

Meakins[3] has recorded an interesting series of cases of jaundice in circulatory failure. He points out that two types of jaundice may occur in this condition: (1) Those which are analogous to hemolytic jaundice in which there is either an excess of the precursor of the bile pigments produced in the spleen or an inability on the part of the liver to transform the precursors into bile pigments or (2) the obstructive type of jaundice where, although the bile pigments are formed from their precursors and secreted into the bile capillaries, they are prevented from passing into the large ducts.

In the first case, a positive indirect van den Bergh test would be expected, whereas in the latter a direct as well as indirect would be obtained. It is to the obstructive type that our patients belong.

It is difficult to understand why bile pigments are unable to enter edematous tissue. The close association with the metallic salts of the glycocholates and taurocholates would lead one to anticipate a ready entrance through the cell membrane, when it is remembered

that these salts are very highly surface active. There is, however, no proof that the pigments are necessarily associated in the blood serum with these salts. Furthermore, we do not know whether the bile salts enter the edema fluid. If it could be shown that such an association occurred, it would be even more difficult to explain why they did not render the cells sufficiently permeable to allow the entrance of the pigment.

Ample data have been published to prove that the size of the molecule need not necessarily influence the selective penetration of a substance. Therefore we cannot assume that these pigments do not enter the edematous cells for reason of size alone.

We can only suggest that the turgor of the cells, due to the edema, may in some way hinder the entrance of the pigment. There are so many factors that need study that at present any adequate explanation of the lack of penetration of bile pigments into edematous cells seems little more than speculation.

Summary. Two cases of ipsolateral edema and contralateral jaundice on the basis of cardiac decompensation following hemiplegia are presented and the relation of this phenomenon to cellular permeability discussed.

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REVIEWS.

Osler's Modern Medicine. Vol. VI. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia. Third edition. Pp. 964; 65 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1928. Price, $9.00.

Osler's Modern Medicine. General Index. Pp. 126. Price, $1.00.

Part I deals with the Diseases of the Nervous System, including an introductory chapter (L. F. Barker); chapters on Diseases of the Motor System (W. G. Spiller); the Combined System Diseases of the Cord (C. K. Russel); Scleroses of the Brain, Diseases of the Meninges (E. Bramwell); Tropical Diagnosis of Diseases of the Brain, Aphasia (J. Collins); Intracranial Tumors, Hydrocephalus (H. Cushing); Acute Encephalitis and Brain Abscess, Epidemic Encephalitis (J. R. Hunt); Diseases of the Cerebral Bloodvessels (H. M. Thomas, Jr.); Diseases of the Cerebral Nerves (E. W. Taylor); Diseases of the Peripheral Nerves (G. M. Holmes); Diffuse and Focal Diseases of the Spinal Cord (E. F. Buzzard and C. P. Symonds); Epilepsy (L. P. Clark); Neurasthenia, the Traumatic Neuroses and Psychoses (C. W. Burr); Hysteria, Migraine, Neuralgia, Professional Spasms, Occupation Neuroses, Tetany (S. E. Jelliffe); Paralysis Agitans, Chorea, Choreiform Affections, Infantile Convulsions, Myasthenia Gravis, Paramyoclonus Multiplex, Periodic Paralysis, Astasia-Atasia, Adiposis Dolorosa (D. J. McCarthy); Syphilitic Diseases of the Nervous System, Amaurotic Family Idiocy (B. Sachs). Part II is composed of a chapter on the Diseases and Abnormalities of the Mind (E. A. Strecker). A perusal of the list of contributors will in itself suffice to convince the reader of the uniform excellence of the whole volume. A thorough and complete index in a separate handy volume is a welcome new departure. R. K.

Acute Infectious Diseases. By Jay Frank Schamberg, A.B., M.D., and John A. Kolmer, M.Sc., M.D., Dr.Ph., D.Sc., LL.D. Second edition. Pp. 888; 188 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $10.00.

This excellent account of the acute infectious diseases by two well-known authorities may be highly praised with safety. This new edition has not only been extensively revised, but a number of new

chapters on diseases not formerly included have been added. The clinical phases of the chapters on vaccinia, smallpox, chickenpox, scarlet fever, measles, rubella and typhus fever have been in considerable part retained. The chapter on diphtheria has been rewritten and new chapters on the prevention of diphtheria, Vincent's angina, serum anaphylaxis, erysipelas, mumps, whooping cough, cerebrospinal meningitis, the "fourth disease" and erythema infectiosum have been added. E. K.

LABORATORY MANUAL OF THE MASSACHUSETTS GENERAL HOSPITAL. By ROY R. WHEELER, M.D., and F. T. HUNTER, M.D. Second edition. Pp. 101. Philadelphia: Lea & Febiger, 1928. Price, $1.75.

THE second edition has been brought up to date and offers in compact form a most useful compendium of laboratory methods. O. P.

GOITER PREVENTION AND THYROID PROTECTION. By ISRAEL BRAM, M.D. Pp. 327; 13 illustrations. Philadelphia: F. A. Davis Company, 1928. Price, $3.50.

THIS volume is intended primarily for the laity, and represents the author's views on the physiology and pathology of the thyroid gland as well as the treatment of simple and toxic goiter. There is an appendix dealing briefly with the other glands of internal secretion. About one-fifth of the book is devoted to an exposition of the author's views on the etiology and treatment of exophthalmic goiter; his unreserved condemnation of surgical treatment in this condition represents a minority opinion. The style is not classic and there is frequent repetition of ideas. The volume does not represent a notable addition to the literature on its subject. E. R.

CHEMOTHERAPEUTIC RESEARCHES ON CANCER. WITH ESPECIAL REFERENCE TO THE LEAD AND SULPHUR GROUPS. By A. T. TODD, M.B. (EDIN.), M.R.C.P. (LOND.), Hon. Assistant Physician, Bristol Royal Infirmary; Lecturer in Pathology, Bristol University. Pp. 127; 11 illustrations. Bristol: J. W. Arrowsmith, Ltd., 1928. Price, 2 s., 6 d.

SEVERAL interesting chemical and clinical studies of the combined effects of colloidal lead and selenium in the treatment of

inoperable cases of cancer, based on the possibility that the combination of the two substances might work more efficiently than either singly and that the analgesic effects of selenium might mitigate the painful effects both of advanced cancer and of the lead treatment. Though the 12 cases abstracted in the first article are meager and entirely inadequate, the improvement noted—always a dangerous criterion for evaluation—appears to the author to justify his expectations.

In a later series of 44 cases, pain was relieved in about one-half and growth retarded in 24 out of 40 cases. E. K.

CLINICAL MEDICINE. By OSCAR W. BETHEA, M.D., PH.G., F.C.S., F.A.C.P., Professor of Therapeutics, Tulane Graduate School of Medicine; Professor of Clinical Therapeutics, Tulane School of Medicine; Chief of Medicine, The Baptist Hospital, New Orleans; Senior Visiting Physician, Charity Hospital of Louisiana; Medical Director of the Standard Oil Company of Louisiana. Pp. 700. Philadelphia: W. B. Saunders Company, 1928. Price, $7.50.

THIS book, being the outgrowth of lectures of a professor of clinical therapeutics, has its emphasis entirely on clinical medicine and therapeutics. Its appeal is therefore somewhat limited. Sections of it might be rewritten with profit, for though there is considerable repetition throughout, the treatment of certain topics is inadequate, notably that of purpura. There is no mention, either, of Small's treatment for rheumatic fever, and only a glancing reference to Minot's treatment of primary anemia. One might take exception, too, to certain statements, as that which describes "benzol as the outstanding medical agent in general use" for leukemias. Within the bounds of its limitations, however, the volume is helpful. There is a wealth of detail on bedside diagnosis and treatment. K. A.

THE DUODENUM. By PIERRE DUVAL, JEAN CHARLES ROUX and HENRI BÉCLÈRE, Surgical Clinic, Faculty of Medicine, Paris. Translated by E. P. Quain, M.D. Pp. 212; 126 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, $5.00.

IN the words of its preface this book is "an exhibition of the information gained in a clinic, the intimate fusion of data acquired by a physician, a surgeon, and a radiologist with the assistance of a chemist," and perhaps no better description of the work can be given. As the expression of the clinical experience of three experts in separate fields working together in the University of

Paris, it is an unusual and noteworthy contribution to the literature on gastroenterology. In particular the book deals with the subject of periduodenitis, the nature of the duodenum in calculous cholecystitis, and the compression of the duodenum by the mesenteric pedicle—all subjects which have heretofore received scant attention. The discussion of these subjects is both illuminating and thought-provoking, though that of the mesenteric pedicle is perhaps less convincing than the others. There is a helpful chapter on the radiological evidence of duodenal ulcer, and one on the surgical technique of duodenojejunostomy. Throughout the book the duodenum appears in a new light: it is no longer thought of simply as a section of the small intestine, but is raised to a position of importance and treated as an entity. A reading of the book leaves one with a clearer conception of the affections of the duodenum, and raises the hope that a number of hitherto obscure ailments of this section of the gastrointestinal tract may be amenable to successful treatment. It closes with an excellent bibliography.

K. A.

Laboratory Diagnosis and Experimental Methods in Tuberculosis. By Henry Stuart Willis, M.D., Johns Hopkins University and Hospital; with a chapter on Tuberculo-complement Fixation, by J. Stanley Woolley, M.D., Loomis Sanatorium, Loomis, N. Y.; Introduction by Allen K. Krause, M.D., Johns Hopkins University. Pp. 330; 25 illustrations. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1928. Price, $3.50.

This compact and neat little volume ably and invitingly treats of tuberculosis from the laboratory standpoint, presenting in readily available form a wealth of valuable material, with much technical detail ordinarily widely distributed. It is also helpful to the clinician, and shows how he can effectively coöperate with the laboratory. The subjects dealt with include: the examination of the various bodily fluids and secretions, the methods of staining and concentrating tubercle bacilli, animal inoculation and the preparation of culture media. The three types of tubercle bacilli and various nonpathogenic acid-fast bacilli are described. Tuberculin tests and tuberculo-complement fixation and other serologic tests are discussed as to their clinical application and value, and the preparation of materials is given. Anatomic methods, for example, by injection of tissues and by tissue culture, are presented. Allergy and immunity are briefly discussed. Much space is devoted to the study of induced tuberculosis in animals, and the different results in guinea pigs and rabbits are contrasted. About a third of the book deals with histologic technique. Laboratory equipment is outlined. An extensive and valuable bibliography and an index are appended.

Under resistance of the tubercle bacillus something might have been said of the effect of chemicals in gaseous form. Potassium iodid to produce tubercle bacilli in the sputum is not objected to. With Abraham Lincoln and Herbert Hoover the author inclines to the split infinitive.

Filled with information, convenient for reference and available for experimenter and routinist, this excellent book by a recognized authority promises to receive a hearty welcome. C. M.

A History of Pathology. By Esmond R. Long, Professor of Pathology, University of Chicago. Pp. 291; 55 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $5.00.

If we accept one of the best definitions of pathology—that it is the study of the effects produced on the body by disease—then its history might easily become coëxtensive with the history of medicine. The author has avoided this pitfall and yet has delved far enough into the roots and borderlines of the subject to exhibit a broad viewpoint and to trace its logical development through the centuries. Incidentally we would have gladly learned when the word pathology first came into use; of course, many centuries before the subject was first recognized as a specialty.

The approach is much the same as in Garrison's *History of Medicine*, to which the author gives high praise. The twelve chapters are devoted to The Pathology of Antiquity; Galen and the Middle Ages; The Pathology of the Renaissance; The Seventeenth Century; Morgagni and the Eighteenth Century; The Paris School at the Opening of the Nineteenth Century; Pathology in England in the First Half of the Nineteenth Century; Rokitansky and the New Vienna School; Virchow and the Cellular Pathology; Pathological Histology and the Last Third of the Nineteenth Century; The Rise of Bacteriology and Immunology and Experimental and Chemical Pathology.

The past century occupies about one-half of the text. The subject matter is well chosen and apportioned, the style forcible, clear and easy and the illustrations are appropriate and for the most part fresh and interesting. Some have unfortunately suffered in the reproduction. "Here is the first definite and systematic account of the subject in English and [that] our author has succeeded in the execution of his plan through his competence, his praiseworthy industry and a spirit ever ready to correct errors pointed out or ascertained." (F. H. Garrison in the Foreword.) We agree absolutely with this and also with the author's statement in the Preface that "nothing gives a better perspective of the subject than an appreciation of the steps by which it has reached its present state."

E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Annals of the Pickett-Thomson Research Laboratory, Volume IV, Part 1. The Pathogenic Streptococci. An Historical Survey of Their Rôle in Human and Animal Disease.** Pp. 250. Baltimore: Williams & Wilkins Company, 1928.

*Thromboangiitis Obliterans.** By GEORGE E. BROWN and EDGAR V. ALLEN, collaborating with HOWARD R. MAHORNER. Pp. 219; 62 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $3.00.

European Clinics. By Editorial Staff of European Clinics, DR. WILLIAM LINTZ, Editor-in-Chief. Pp. 347; illustrated. Philadelphia: J. B. Lippincott Company, 1928. Price, $5.00.

A report of the clinics given the 125 doctors comprising the Interstate Post-Graduate Assembly of North America, during their visit to England, Scotland, Norway, Sweden, Denmark, Germany and France in 1927. An enthusiastic introduction by the editor stresses the high value of the clinics, which were given by men of high-caliber, covering a wide range.

*Mineral Waters of the United States and American Spas.** By WILLIAM EDWARD FITCH, M.D. Pp. 799; 37 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $8.50.

*Partnership, Combinations and Antagonisms in Disease.** By EDWARD C. B. IBOTSON, M.D. (LOND.), B.S. Pp. 348. Philadelphia: F. A. Davis Company, 1929.

*The Kahn Test. A Practical Guide.** By R. L. KAHN. Pp. 201; 7 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $4.00.

*The Fuel of Life.** By JOHN JAMES RICKARD MACLEOD, M.B., LL.D., D.Sc., F.R.C. Pp. 147. Princeton: Princeton University Press, 1928. Price, $2.50.

*Diabetic Surgery.** By LELAND S. MCKITTRICK, M.D., F.A.C.S., and HOWARD F. ROOT, M.D. Pp. 269; 81 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $4.25.

*Contribution a l'Étude des Spirochetides.** By DR. AUGUSTE PETTIT. Pp. 651; 154 illustrations. Vanves (Seine) Chez l'Auteur, 1928. Price, $4.00.

*Diseases of the Blood.** By A. PINEY, M.D., M.R.C.P. Pp. 195; 20 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, $4.00.

Progressive Medicine. Volume IV, December, 1928. Pp. 424; illustrated. Philadelphia: Lea & Febiger, 1928.

NEW EDITIONS.

Alcohol: Its Action on the Human Organism. Issued by the MEDICAL RESEARCH COUNCIL. Distributed in United States by BRITISH LIBRARY OF INFORMATION, 5 East 45th Street, New York City. Second edition, 1928. Pp. 170. Price, 30 cents.

A nonpartisan representation by eminent investigators.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Heart during Anesthesia.—Marvin (*New England J. Med.*, 1928, **199**, 547) discusses in a very interesting paper the question of operation upon the patient with the damaged heart. This is a perennially active subject of discussion among surgeons and physicians, and the author, from his experience in a large number of heart cases, draws conclusions which seem to be most sane and sensible. In a certain number of cases operation is a necessity in order to save the patient's life, and the cardiac condition must be considered from the point of view of doing all that can be done without injury to the organ. In a goodly number of cases, however, operation might be of great benefit to the patient, although not indicated absolutely. Under such circumstances it should be borne in mind that when a patient is able comfortably to carry on the activities of a normal life the examination which discloses a damaged heart should not alter the decision as to operation. On the other hand, if early congestive failure is present, basing the decision largely on the subjective symptoms of the patient, then the query arises as to whether to operate or not. In these patients, with proper teamwork between the surgeon and physician, operation can be safely carried through to successful termination. Even in patients with advanced congestive failure, rest, digitalis and diuretics will make the operation successful. The choice of the anesthetic to be given to a heart patient is important, but here, almost as nowhere else is it necessary to employ a skilled anesthetist. Nitrous oxid and ethylene are the anesthetics of choice. When given properly there is absolutely no stress or strain on the heart, and the patient comes through without very much more cardiac strain than if he had sunk into a quiet

and restful sleep. Three cardiac conditions are likely to cause sudden death even when the patient is at rest. Syphilitic heart disease with aortic insufficiency, angina pectoris and heart block are cardiac disabilities which should be considered seriously when operation is required. The patient should be warned that sudden death might occur at any time and the slight stimulus of operation might be sufficient to bring about a fatal termination.

Bronchography According to the Passive Technique: the Method of Choice for the Roentgenologist.—OCHSNER (*Radiology*, 1928, **11**, 412) refers briefly to attempts of the past to visualize the alignment of the tracheal-bronchial tree and then discusses the indications for bronchography. The methods that we employ at the present time are, for the most part, rather difficult in technique, and those which are not difficult in technique require the coöperation of a bronchoscopist. The method which he uses is technically simple and can be done by any individual. The mouth is cleansed with an antiseptic mouth wash and then the anterior surface of the anterior tonsillar pillar is painted with a 10 per cent cocain solution, from the uvula to the angle between the anterior pillar and the tongue, anesthesis being continued until the swallowing reflex is abolished, as shown by immobility of the larynx upon attempted deglutition. The patient is then given 3 to 4 cc. of a 3 per cent novocain solution. He is instructed to tip the head backward, protrude the tongue and breathe. Novocain acts as an anesthetic to the tracheobronchial mucosa. The anterior pillars are again painted with a 10 per cent cocain solution, and the patient placed behind the fluoroscopic screen. He is given 10 cc. of iodized oil in a glass, the head is held backward and he is instructed to take a deep breath and while inhaling pour the oil into the mouth. With the abolition of the swallowing reflex, the oil may be seen flowing from the trachea down to the bronchial tree. An additional 10 cc. is given and in a minute or two it may be seen filling the bronchi, the smaller bronchi and the bronchioles. Confirmatory evidence may be obtained and permanent record made by taking a roentgenogram. The method is extremely simple and may be carried out by anyone who has had no special training with intralaryngeal manipulation. Furthermore, the mode of filling may be observed under the fluoroscope and yields valuable diagnostic information. The method may be also used for the treatment of bronchiectasis and was found to give very excellent results in a considerable series of cases.

Infection of Laboratory Worker with Bacillus Influenzæ.—WALKER (*J. Infect. Dis.*, 1928, **43**, 300) writes that Pfeiffer's bacillus is frequently present in respiratory-tract infections. It is difficult, however, to determine whether the organism is the primary cause of infection. In the present report an accidental infection with Bacillus influenzæ occurred in a laboratory worker. The course of the infection is described. Rhinitis, conjunctivitis and bronchitis were the outstanding features. There was no fever. The course of the infection demonstrates that certain strains of the "organism," at least, have an extraordinary avidity for attacking the respiratory mucous membrane as the primary cause of disease.

SURGERY

UNDER THE CHARGE OF

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Congenital Malformations of the Mesentery—A Clinical Entity.—Waugh (*Brit. J. Surg.*, 1928, **15**, 438) says that congenital malformations of the mesentery are a definite morbid entity of a chronic type which may be recognized before operation by careful clinical investigation. The symptom complexes to which they give rise cannot be explained by reference to any of the well-known abdominal surgical diseases. The most important physical sign is emptiness of the right iliac fossa associated sometimes with an asymmetrical enlargement of the abdomen on the left side. These signs follow of necessity, inasmuch as the whole segment of the embryonic midgut is involved in a failure of rotation and fixation after reduction from the umbilical sac. Radiological investigation should prove to be more helpful in confirming the clinical diagnosis when the special method of barium by mouth for the small intestines and a concomitant barium enema for the large bowel is followed routinely. Operative treatment may cure the patient; alternately it may reveal a pathologic condition for which a rational course of treatment may be drawn up subsequently, when the precise details of the malformation have been discovered.

Cholecystitis—A Clinical and Experimental Study.—Wilkie (*Brit. J. Surg.*, 1928, **15**, 450) claims that in the vast majority of cases of chronic cholecystitis in the human subject, the bile is sterile on culture. Cultures of the whole thickness of the gall-bladder wall most frequently give no growth. Cultures from the submucous and outer coats, leaving the mucosa intact, have given a growth of streptococci in 42 per cent of cases. Bile has been shown to inhibit the growth of these streptococci. The lymph gland along the cystic duct in cases of cholecystitis has been shown to yield a growth of streptococcus in 86 per cent of cases. Bacillus coli was recovered from the bile in only 6 per cent of cases. In the one case in which this organism was recovered from the cystic gland contamination by bile could not be excluded. The streptococcus of cholecystitis is a short-chained type, produces smooth, nonhemolytic colonies on agar and grows readily on glucose broth. Injections of saline suspensions of this organism into the lumen of rabbits' gall bladder produced no change. Intramural injections of streptococci into rabbits' gall bladders produced a progressive chronic cholecystitis from which the organism was readily recoverable. With the cystic duct ligated intramural injections produced a chronic empyema with marked intramural changes. Small calculi were produced with

both types of intramural injection. When the cystic duct was ligated, the calculi contained calcium and cholesterin, when the cystic duct was patent—cholesterin only. Intravenous injection of the streptococci, when repeated, produced a progressive chronic cholecystitis with the formation of cholesterin stones. Separation of the gall bladder from the liver with interpolation of the omentum to exclude infection by lymph spread from the liver, along with ligation of the cystic duct, did not prevent the development of cholecystitis when streptococci were injected intravenously. The intramural pathologic changes produced experimentally, resemble in every detail the changes seen in the human gall bladder in cholecystitis. Cholecystitis would appear to be a blood-borne streptococcic, intramural infection.

Exostoses Occurring in the Os Calcis as the Result of Gonococcal Infection.—WADE (*J. Uro.*, 1928, **20**, 259) claims that primarily the causative organism is the gonococcus. Dorsey reports that the gonococcus has been found in spurs. The present author, however, has failed to demonstrate the organism in the osseous deposit. The pathology that occurs is evidently first a periostitis occurring at or near the attachment of the plantar fascia and the attachment of the tendo Achilles followed by a deposit of calcium salts in the sheaths of the tendons. Some contend that a bursitis is the primary pathology with the subsequent spur formation. Many of the patients who are badly disabled by gonorrheal rheumatism are truly sufferers of gonorrheal spurs and after all of the infection in the genitourinary tract has been eliminated, the existing disability may be terminated by removal of the spurs. For a complete recovery after operation the patients must have the focus of infection entirely removed. Spurs may quickly recur in the event of a subsequent infection. Trauma and flat feet play an important part in the production of spurs. Spur formation can be prevented in the stage of periostitis by placing the parts at rest and by well directed local treatment. Sodium iodid intravenously is of great service in this stage. The incision of choice is the one directly down upon the point of pathology.

Thyroid Adenomata.—ROGERS (*Am. J. Surg.*, 1928, **5**, 265) claims that there are two varieties of thyroid adenomata: (*a*) True, interstitial or fetal and (*b*) pseudovesicular or colloid, "colloid nodules." These terms have regard for the nature and probable origin of the tumors. The fetal tumors occur in young subjects and are hard encapsulated bodies either single or multiple. They are true blastomata. The colloid nodules occur in older women; they are always multiple. They are not true blastomata, but degeneration nodules which become encapsulated by a process of vesicles distended with colloid in groups, intervening between which other vesicles are compressed and distorted until ultimately they form capsules around each of the growing nodules. Either variety of adenoma may become cystic. Adenoparenchymatous goiter is very common. It almost invariably occurs in women. This form may be toxic and may produce pressure at the root of the neck. One or both thyroid lobes may be affected. Adenomata, whether occurring singly or in numbers, are treated by resection—enucleation, the essential details of which procedure are given in the paper.

THERAPEUTICS

UNDER THE CHARGE OF

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Cistern Puncture in the Treatment of Cerebrospinal Meningitis.—Following upon the work of Ayer, Hartwich, Peet and others, PALSCO (*Wien. klin. Wchnschr.*, 1928, **41**, 1182) reports his experiences in the successful treatment of two severe cases of cerebrospinal meningitis by cistern puncture and the injection into the cistern of antimeningococcus serum. Only four other cases similarly treated were found by him in the literature. He discusses the rationale of this method of treatment emphasizing the fact that it assures an effective and complete distribution of the serum throughout the subarachnoid spaces of the brain and even into the brain, ventricles which is not the case following serum administration by lumbar puncture. He says that the method proves comparatively simple, especially when opisthotonus has not developed to a degree sufficient to prevent placing the patient in a sitting position. Not only is the serum distribution more complete and effective than by lumbar puncture, but drainage also is more effective, and in those cases where a block has developed it would seem to be the only satisfactory method of treatment. Injection of serum into the cistern does not seem to be associated with danger of injury to the pons or medulla. This method of injection is usually followed by severe headache, sweating and vomiting which, however, rarely last for more than ten to twenty minutes and are not sufficient to outweigh its many advantages.

The Treatment of Syphilitic Diseases Including That of the Central Nervous System with Sulphur Oil.—Following his successful treatment of 4 out of 7 patients with general paresis, SCHROEDER (*Klin. Wchnschr.*, 1928, **7**, 1636) endeavors to determine whether sulphur oil has true antisyphilitic actions or whether the beneficial effects in general paresis are due to its property of producing a febrile reaction analogous to that produced by malaria inoculation. He reports several small groups of cases of primary, secondary and tertiary syphilis which he treated by the intramuscular administration of sulphur oil without the use of recognized syphilitic drugs. He concludes from the effects in these cases that sulphur oil has a definite and rather marked specific antisyphilitic action in all stages of the disease. Although this agent brings about a change in the Wassermann reaction from positive to negative, this change is not permanent in all cases. He feels that sulphur oil cannot, therefore, be regarded as a satisfactory agent for the treatment of syphilis when used alone and thinks that it should be used only in conjunction or alternating with recognized antisyphilitics. He notes in addition to its beneficial effects, which seem especially well marked in syphilis of the central nervous system, that it seems to be well borne in the presence of severe vascular disease and in pregnant

women. In the latter, however, it must be administered carefully in order to avoid a marked rise of temperature. In view of the demonstration of antisyphilitic action by sulphur oil, the author raises the question as to how far one should go in the endeavor to produce a marked febrile reaction, although he admits that in certain cases such as general paresis such a reaction is apparently of itself a valuable therapeutic measure.

Alcohol Injection in the Treatment of Gangrene.—HANDLEY (*Brit. Med. J.*, 1928, ii, 593) discusses the value and the serious disadvantages of Leriche's periarterial sympathectomy in the preventative treatment of gangrene, and contends that the periarterial injection of alcohol is equally effective and is devoid of many of the disadvantages of the Leriche operation. The technique is not difficult. The exposed artery is injected at four points around its circumference with 2 to 3 minims of alcohol at each point. The finest possible needle is employed and is introduced obliquely and nearly parallel with the long axis of the artery. This injection produces a white band about ½ inch wide encircling the vessel. The effects are immediate, and the initial constriction present in the Leriche operation is absent, there being no vasoconstriction, but, on the contrary, immediate distal dilatation. This fact is of particular value in cases where gangrene is threatened. The effects of the Leriche operation last for only a few weeks, while the dilatation secured from injection may last for more than a year. The one great disadvantage of alcohol injection is the fact that its results are uncertain, probably due to anatomic differences in the distribution of the vasomotor nerves, so that occasionally no dilatation at all ensues. The indications for its use are not well established, but since it is probably safe its trial is justified wherever it seems to be indicated. It may be recommended in cases of threatened or incipient senile gangrene of a lower extremity, and should, if possible, be employed in the prodromal period. It seems to be useless in Buerger's disease, and is of doubtful use in Raynaud's disease.

Histamin Action and Blood Regeneration.—In an endeavor to throw some light on the problem of the nature of the substance in liver extracts which is responsible for blood regeneration, J. PAL (*Deutsch. med. Wchnschr.*, 1928, **54**, 1544) having observed that some of those liver extracts employed for their depressant action on the blood pressure also produced notable blood regeneration, undertook to study other tissue extracts and found that those containing histamin all produced blood regeneration. Similarly, he finds that small doses of histamin itself stimulate the regeneration of the red cells in pernicious anemia, in secondary anemia and even in normal persons. Along with this effect on blood regeneration there is also a stimulation or a restoration of the failing appetite just as with the administration of liver itself or the effective extracts. From these observations, he concludes that histamin is, perhaps the most important, of the substances responsible for promoting regeneration of the blood. He also concludes that blood regeneration is itself the factor that is responsible in anemic and cachectic patients for stimulation of appetite and the improvement in their general well being.

PEDIATRICS

UNDER THE CHARGE OF

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Newer Aspects of Acidosis.—MARRIOTT and HARTMANN (*J. Am. Med. Assn.*, 1928, **91**, 1675) state that the contributing factors in acidosis are increase of normal acids such as lactic, phosphoric and sulphuric; the loss of fixed base; and maintenance or failure of maintenance of normal osmotic pressure. The explanation of the means by which such factors operate lies in the effects of dehydration due to diarrhea, vomiting or polyuria; abnormal metabolism giving rise to abnormal organic acids, and failure of the kidney because of oliguria or actual renal injury to adjust by urinary secretion for such changes. Water loss due to diarrhea would naturally be expected to increase the concentration of all solutes in the plasma except those which may be secreted in the gastrointestinal canal and into the urine. In the dehydration accompanying severe diarrhea oliguria occurs, so that loss of solute by the urine may be neglected. There apparently occurs loss of base bicarbonate by way of the bowel because of its secretion from the plasma into the pancreatic and intestinal juices. The early picture of the anhydremia is brought about chiefly by water and base bicarbonate loss in the stool. Where the dehydration is caused solely by vomiting as in pyloric or high intestinal obstruction, there occurs a loss of gastric juice which contains hydrochloric acid and a small amount of fixed base. A dehydration of this sort would give rise to a diminished base chlorid content of the plasma with increase in base bicarbonate or an alkalosis. If dehydration is brought about largely by a polyuria as in diabetes, the urine carries out not only dextrose and water but also important salts. The loss of these substances is important in producing diabetic acidosis. In severe chronic nephritis, urinary secretion is at fault as a result of renal injury, and acids such as phosphoric and sulphuric are insufficiently removed. There also occurs a loss of fixed base from the plasma in excess of the usual loss. This is due to a failure of the kidney to substitute ammonia for the fixed base of the plasma salts and secondarily from failure of the kidney to maintain the normal maximum hydrogen-ion concentration of the urine.

Healing in Infantile Scurvy as Shown by X-ray.—MCLEAN and MCINTOSH (*Am. J. Dis. Child.*, 1928, **36**, 875) in a long paper enumerate the types of disturbances found by Roentgen rays of the long bones in infants with scurvy, and describe the changes during the process of healing. In 115 roentgenologic examinations of 52 patients with scurvy particular reference was made to the variation in the picture according to the stage of the disease. The relative value of the Roentgen ray signs of scurvy from the viewpoint of diagnosis in acute cases and the relative frequency of the various signs presented for all stages are shown

in their tabulations. They found it necessary to take the rachitic factor into consideration as its presence often modifies the scorbutic picture. They found a decided tendency for the scurvy to heal by the laying down of new lines of calcification. Hematoma of large size was noted to have left their mark as long as three years in the form of unilateral thickening of the shaft. Disturbances of nutrition may alter the rate though not the general order of the changes. These changes vary from fibrous tissue trabecular changes through to calcification.

The Preventorium Child.—Bronfin (*Am. J. Dis. Child.*, 1928, **36**, 931) reviewed the records of 300 preventorium children and made a study of the roentgenograms. An underweight of 7 per cent or more was found in 70 per cent. In 45 per cent definite cervical or submaxillary lymphadenitis was noted. In 30 per cent, fever was a prominent symptom. An appreciable difference was not observed in the symptomatology or physical signs between the tonsillectomized and the nontonsillectomized groups. The greatest incidence of clinical disease and positive physical signs was noted in those with a history of definite exposure. Physical signs were often negative when the history and symptoms pointed to active disease. The Roentgen rays were of the greatest importance in diagnosis when correlated with the other symptoms. Of the entire series, only 72 roentgenograms of the chest were considered within the normal. Calcification at the hilum, strongly suggestive of tuberculosis, was observed in only 22 per cent, but it is believed that the incidence would have been greater if films in the oblique position had been taken. Primary foci were detected in 11.6 per cent, and in 11.3 per cent there was noted frank parenchymal pulmonary infiltration. Attention was called to the difficulty in making a diagnosis of tracheobronchial tuberculosis, which in this series was frequently responsible for active symptoms and was often attributed to other causes. Under treatment, symptomatic improvement invariably occurred. Unremitting supervision was necessary for in many patients there was a recurrence of symptoms with increased physical activity. A notable recession was not noted in either the cervical or the tracheobronchial glands after prolonged periods of continued heliotherapy.

A Clinical Study of Enuresis.—Bleyer (*Am. J. Dis. Child.*, 1928, **36**, 989) says that a clinical study of certain factors commonly held accountable for enuresis failed to show their relations to this disease. Cures in this series of cases amounted to about 80 per cent and were accomplished without regard to any of these factors by measures directed to the bladder itself. A study of the incidence of enuresis in relation to sex suggests that the cause of this disease does not exist in any anatomic or physiologic peculiarity external to the opening of the bladder. The rôle of the voluntary nervous system is unimportant in enuresis. This disease is a disturbance of the physiology of micturition, probably due to stimuli arising in the bladder itself which for the time being place it beyond the control of the will. Discipline plays no part in true enuresis, since this disease does not owe its origin to a lack of discipline nor is it controlled by this measure. In conformity with the definition evolved in this study, the term enuresis vera is suggested to

indicate that type in which dissociation between the brain and the voluntary nervous system, as concerns the physiology of micturition, actually appears to exist, and the term pseudoenuresis is reserved for that type of defective control which can be relieved by measures designed to influence the will or to obtain the coöperation of the child. Atropin and massage of the bladder were the only measures found to be effective in the treatment of true enuresis.

Restlessness in Infancy.—Lippman (*J. Am. Med. Assn.*, 1928, **91**, 1848) recommends certain measures to control restlessness in infancy. Every attempt should be made to insure the mother rest and relaxation in a peaceful environment. The presence of the child in the home should not preclude other emotional outlets for the parents. The greater share of the management of the restless infant, as far as is practical and possible, should be turned over to other persons than the parents. Frequent dietary changes may be necessary before the ideal food or schedule can be realized. Every reliable known means of relieving air swallowing should be utilized, even to the extent of temporary removal from the breast. The measure of placing the infant to the breast in a drowsy sleepy state should be employed. The suggestion of using chloral to produce this sleepy state should be considered. Atropin should be used. The author urges its use up to the point of tolerance.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Alopecia Areata.—Pusey (*Arch. Dermat. and Syph.*, 1928, **17**, 701) has recently briefly reported a case of alopecia areata apparently the sequel of severe emotional stress and nervous shock.

Industrial Dermatoses.—The lesions are classified by Foerster (*Arch. Dermat. and Syph.*, 1928, **17**, 585) into toxicodermias, involving a sensitization factor, localized occupational dermatitis, limited to sites of contact with the irritant, and occupational eczema, which persists, extends and recurs after the exciting cause is removed. Periodic inspection, physical examination before employment and the building up a selected, resistant personnel in occupations involving irritants are emphasized. Treatment at the onset should be properly planned, for prolonged attacks often follow the injudicious use of irritant routine

first-aid applications. A complete cure of the first attack is important to prevent relapse and chronicity. Cleanliness, obtained by making the clean-up time part of the working hours, has great prophylactic value. The investigation of the systemic background of the individual case is as important in industrial as in nonoccupational dermatoses. "Compensation is not dependent on any implied assumption of perfect health" in the worker. The mere fact of hiring him is a presumption of good health, and his dermatoses of occupational origin are, therefore, compensable even though a predisposing cause antedated his employment. In the discussion of this paper, the influence of carriers and disseminators of pyogenic infection was emphasized, and the value of rotating workers through short periods in jobs involving contact with irritants. The necessity for the dermatologist and the industrial physician knowing the trade processes as well as the medical aspects of industrial cutaneous disease was also stressed.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Kidney Destruction by Irradiation.—One of the most unpleasant sequels of the radical operation for the removal of uterine cancer is the development of a urinary fistula as the result of injury to one of the ureters. If the fistula does not close spontaneously after a fair period of time, there are two choices for the patient, plastic operation on the ureter, including various types of implantation into bladder or bowel, and removal of the corresponding kidney. In many cases an attempt to treat the fistula by a conservative procedure is out of the question on account of the extent of the primary operation and the hazard which would accompany a secondary operation in such a field so that if the patient is to be relieved it must be by removal of the kidney. It has been shown by animal experiments that if sufficient irradiation of the Roentgen rays be given to the kidney, its function will be seriously impaired and finally cease altogether. Applying this fact for the first time to the human being, KLEIN (*Zentral b. f. Gynäk.*, 1928, **52**, 1500), of Prag, reports that in 4 cases of ureteral fistula following the Wertheim operation, which could not have been helped except by nephrectomy, irradiation was given to the kidney on the side of the injury and in each case the urinary excretion ceased and the patient became entirely relieved of her trouble. This is a form of therapy which is well worth

remembering because none of us can tell when we might have a case of ureteral injury on our hands in which the risk of further surgery might be attended with too much danger and it would be very comforting to know that such cases have been entirely relieved by Roentgen ray treatment of the kidney.

Pelvic Inflammatory Disease.—On several previous occasions, we have discussed the variable views in regard to the surgical treatment of pelvic inflammatory disease and have quoted the opinions of leaders in the profession both in this country and in Great Britain but have apparently overlooked some of the reports coming from Central Europe. It is of considerable interest therefore to refer to a well-prepared report which has been presented by SZTEHLO (*Zentralbl. f. Gynäk.*, 1928, **52**, 2233) of Budapest. The report is based upon 233 patients who were operated upon for suppurative pelvic inflammatory disease in his clinic, of which Lovrich is chief, during a period of fourteen years. In the acute stage of the disease, they do not operate except upon vital indications. In the chronic stage, they operate upon patients who have been free from any fever for a period of from six to twelve months and then only after a thirty- to forty-minute treatment with diathermy produces no febrile reaction. All of the operations are performed by the abdominal route, never by way of the vagina. In most of the cases that are operated upon, conservative surgery is the rule, only in rare instances is the uterus removed by supravaginal hysterectomy and in no case have they performed complete hysterectomy. In removing the tubes, the wedge excision of the cornual portion is always performed. Vaginal drainage is employed if the abscess sac is ruptured during removal and pus is spilled or when satisfactory peritonealization cannot be accomplished and also in those cases where there is bloody oozing which cannot be controlled by other means. While the blood-sedimentation test has been used frequently to determine when the patient is ready for operation, the results have not by any means been what could be desired since more than half of the patients who died following operation had a sedimentation time of over an hour. He believes that the result of the operation cannot be predicted by any test and does not depend entirely on the virulence of the bacteria, the asepsis or technique of the operation but upon the unknown factor of the resistance of the individual patient. As a demonstration of this point he cites 2 cases which were operated upon on succeeding days for the same condition. Both had the same preoperative preparation, normal blood findings and a sedimentation time of over an hour and gave no febrile reaction following diathermy. At operation bilateral pus tubes were removed in each case. One patient had hemolytic streptococci in the pus and she made an afebrile recovery; in the other patient only sterile pus was obtained but she died on the third day from symptoms of general peritonitis. In this series of 233 cases there were 10 deaths (4.3 per cent mortality) and the operations performed consisted of removal of one adnexa in 19.3 per cent, removal of both adnexa in 61.6 per cent, removal of one adnexa and the opposite tube in 10 per cent and supravaginal removal of the uterus in 9.1 per cent. Satisfactory postoperative results were obtained in 89 per cent of the cases and secondary operation was called for in only one case (0.4 per cent). The good postoperative results are

largely attributed to the frequent employment of vaginal drainage, it having been employed in over half of the cases. The following table, presenting the mortality experience of several European clinics will be of interest to the American gynecologist:

	Per cent mortality.
Thaler, 108 radical operations	8.6
Thaler, 262 conservative operations	5.3
Werner, 193 radical operations	6.7
Werner, 94 conservative operations	2.1
K. Fraenkel, 372 radical operations	6.6
Frigyesi, ? radical operations	7.5
Frigyesi, ? conservative operations	4.5

Sarcoma of the Uterus.—In an investigative search for information relative to sarcoma of the uterus MILLER and ROGERS (*New England Med. J.*, 1928, **198**, 927) have gone over the records of the Massachusetts General Hospital for the period from 1876 to 1926 and found 25 cases of sarcoma of the uterus, constituting 1.4 per cent of the number of uterine fibroids which were observed during that time. They found that sarcoma of the uterus presents no pathognomonic signs or symptoms and is usually mistaken for myoma. It may, but does not necessarily originate in a preëxisting myoma but any rapidly growing fibroid tumor should be suspected of being sarcomatous. At every operation for fibroid tumor the specimen should be carefully examined to determine if sarcoma be present and if so the operation should be made very radical. In this series the chief symptoms were bleeding in 68 per cent, pain in 52 per cent, abdominal tumor in 40 per cent and loss of weight in 12 per cent. In the follow-up study, 48 per cent were not traced and but 4 per cent were well six years after the operation.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Ocular Complications of Diabetes.—GIFFORD (*Med. Clin. North America.*, 1928, **12**, 423) states that true diabetic cataract may occur, but is rare, while senile cataract occurring in the diabetic is common and does not differ from cataract in the nondiabetic. With a little preoperative care to reduce the urinary sugar to the minimum, operation in these cases is not attended by any great risk. What may be called a true diabetic cataract is characterized by the appearance of fluid vacuoles under the capsules of both lenses, which progresses rapidly to complete opacity in periods of a few weeks to six months. There may be an occurrence of changes in refraction during the course of diabetes. When the blood sugar becomes suddenly high, the osmotic pressure of the

blood becomes low through the pouring of the fluid into the blood from the tissues and the loss of sodium chloride from the blood. This fluid of low osmotic pressure is able to penetrate the lens capsule, causing the lens to swell, with resulting myopia. If blood sugar is lowered, the lens gives up the water, becomes flatter than normal, with resulting hyperopia. The serious change in diabetes is diabetic retinitis. Two types of lesions are seen, white patches which are usually small and single, seen in the central region and around the nerve. Hemorrhages along large vessels are not far from the nerve head. The author refers to the paper of Wagener and Wilder, they reporting that retinitis was not seen in the severe forms of pure diabetes but the mild, easily controlled cases with some evidence of vascular disease, and the retinitis was due to arteriosclerosis. Author finds nothing in this article on which they based their findings as to the vascular origin of the retinitis. Since this report American ophthalmologists may have been inclined even to doubt the existence of pure diabetic retinitis. The presence of retinitis in a diabetic does not indicate a particularly grave prognosis in cataract as does albuminuric retinitis.

Oculogyric Crises in Chronic Epidemic Encephalitis.—McCowan and Cook (*Brain*, 1928, **51**, 283) state that it is doubtful if the tonic eye spasms, termed by the French, crises oculogyres, occurred before 1923. The incidence of these cases is increasing. In this series of 23 cases taken from a total of 136 cases of encephalitis the earliest case commenced in 1923 and the earliest epidemic which lead to a case was that of 1919. The shortest interval between the acute attack and the appearance of the crisis has been a few months and the longest eight years. All cases are associated with Parkinsonism, the onset preceding that of the crises. Age and sex are unimportant. Other ocular symptoms are not more frequent than in ordinary encephalitis without crises. The crises are in the nature of tonic seizures not always confined to the eye muscles but frequently involving the muscles of the head and neck. Pain is an unusual concomitant, but physical distress of various kinds is very common. The eyes may become fixed in any position and this position may change during a crisis or between crises. In one case the eyes took a position of forced convergence and in three a fixed stare to the front. This variability is important in determining the site of the lesion. The most common position is either straight up or upward and to either side. The eyes may remain fixed from a few seconds to several hours. Fatigue is an important factor in the onset of the attacks because they occur most often in the afternoon or evening. Usually there is no obvious exciting cause. It is occasionally possible to shorten or prevent attacks and suggestion is the most potent agent in this respect but it is misleading to regard these cases as hysterical in nature because the increased suggestibility of the encephalitis is due to an interference with normal cortical control and a cutting off of its inhibitory influence. The casual lesion of oculogyric crisis lies in associational mechanism situated above the four supranuclar centers subserving conjugate movements the theory being accepted that there is a supranuclear center for lateral conjugate movements and one for vertical movements on each side. In a certain number of cases the crises tends to disappear with time and this is especially true in those treated with hyoscin hypodermically.

OTO-RHINO-LARYNGOLOGY

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Gross and Microscopic Pathology in Twenty-three Consecutive External Frontal Ethmosphenoid Operations.—SIMPSON and HARRIS (*Ann. Otol., Rhinol. and Laryngol.*, 1928, **37**, 452) found in all cases a hyperplastic submucosa infiltrated with all types of acute and chronic inflammatory cells, as well as periosteal thickening. Most cases revealed many submucosal thrombotic bloodvessels. In several instances ulceration of the mucosa was seen. Metaplasia occurred in those cases of prolonged chronic irritation. Grossly, of the 23 cases, periostitis occurred in 20, polypi in 12, osseous necrosis to point of perforation in 3, cysts in 2, and osteoma in 1. A brief résumé of each case is given. Some of the cases, which were clinically chronic, were found to present microscopic evidence of acute inflammation, and, *vice versa*, in one acute case much evidence of chronic pathological change was encountered. The authors believe that some acute processes are only acute exacerbations of a chronic condition.

Cystologic Examination in the Diagnosis of Infection in the Nasal Accessory Sinuses.—Convinced that the macroscopic examination of washings from the paranasal sinuses is not a trustworthy diagnostic procedure, and basing the rationale of his method on the fact that cellular elements are absent in the irrigating fluids from normal sinuses, SEWALL (*Ann. Otol., Rhinol. and Laryngol.*, 1928, **37**, 642) describes the technique of irrigation of the maxillary sinus as a means of obtaining material for microscopic examination of the antral contents. In the interpretation of the cytological picture on the glass slides as indicative of the pathologic lesion in the sinus, he relies on the predominance of polymorphonuclear leukocytes as pointing to an acute inflammatory process, and of mononuclear forms as suggesting less acute inflammation. Certain technical sources of errors are discussed. The author states that, although the method may become a useful diagnostic procedure in all the paranasal cavities, he has employed it in only the maxillary and sphenoidal sinuses. He considers it as an adjunct in diagnosis of sinus disease, along with such other important aids as history, symptoms, physical findings and Roentgen ray.

Otologic Observations in Trauma of the Head. A Clinical Study Based on 42 Cases.—Disregarding their medicolegal aspects, injuries to the head comprise a most important and alluring field in medicine and surgery—a field which, either directly or indirectly, embraces virtually all departments of medical activity. In analyzing the otologic manifestations in a series of 42 cases, GROVE (*Arch. Ololarynol.*, 1928, **8**, 249) discusses various mechanical, anatomic, pathologic and clinical phases of head traumata. He emphasizes the importance of examination

as soon after the injury as possible, and also at regular intervals over a considerable period. The severity of the trauma does not bear any direct relation to the development or degree of cochlear and vestibular symptoms. Within the temporal bone hemorrhages were found to be the outstanding lesion. Hemorrhage from one or both ears occurred in 9 cases and indicates a longitudinal fracture of the temporal bone. Such cardinal symptoms of vestibular injury as vertigo and spontaneous nystagmus were encountered and carefully analyzed. Deafness was complained of in 14 instances and was found in 31, of which 28 had symptoms referable to the vestibular apparatus. Complete unilateral deafness occurred once. Headache was the commonest complaint.

RADIOLOGY

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Cholecystography.—From their experience with the oral method in 1500 patients, LOCKWOOD and SKINNER (*Radiology*, 1928, **11**, 7) conclude that neither hyperchlorhydria nor achlorhydria have any effect on the shadow of the gall bladder. In 70 per cent of the patients with pernicious anemia cholecystography indicated disease of the gall bladder, 39 per cent having stones; several of the patients improved after operation. Of patients having myocardial degeneration 71 per cent responded abnormally to cholecystography. In cases of infectious arthritis, 69 per cent had cholecystographic evidence of gall bladder disease and 15 per cent exhibited shadows of stones.

Metrosalpingography with Iodized Oil.—Introduced by Sicard and Forestier in 1922, the roentgenography of the uterus and tubes after injection of iodized oil has been of great service. RUBIN and BENDIC (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 348) remind the reader that by this means the uterus and tubes are not seen, but a perfect cast of their cavities is demonstrated. The uterine cavity is triangular in shape, the intrauterine diameter averaging about 4 cm. in width, the narrowest portion being at the internal os. The length of the uterine cavity is about 5 cm. when the uterus is subjected to a pressure of about 100 mm. of mercury. The tube consists of two parts—the isthmus and the ampulla. The isthmus is divided into an intramural portion and the isthmus proper. The ampulla can be divided into the ampulla proper and fimbria (or infundibulum). The short intramural portion of the tube varies from 0.5 to 1.5 cm. in length and is often constricted

at each end. It usually curves downward and outward but the writers saw no multiple curves and angles as described by certain authors. The isthmus proper is seen as a narrow band, often hairlike, sometimes 2 mm. broad. It varies in length from 3 to 10 cm., the average being about 5 cm. Its direction is usually downward and outward and it seldom exhibits any angulations. The ampulla is much wider and always appears irregularly coiled. Its usual width is about 5 mm. and in length it varies from 4 to 10 cm. The fimbria can be seen as a triangular mass, often having on one side a concavity corresponding to the surface of the ovary.

Radium Treatment of Tonsils.—Comparing radium treatment with tonsillectomy, WILLIAMS (*Am. J. Roent. and Rad. Ther.*, 1928, **19**, 334) thinks that the advantage rests with the former. Tonsillectomy entails the use of an anesthetic and the shock of operation; other tissues may be removed; hemorrhage, infection or great soreness in the throat may result, and a week or more may be required for recovery. Radium treatment avoids the use of an anesthetic and is painless; causes no shock, hemorrhage, infection, or pulmonary complications, and the patient's occupation is not interrupted. Radium has a wider field of usefulness than that covered by tonsillectomy in that it can be employed for patients who are not good operative risks, and, what is also important, for treating diseased lymphoid tissue in the pharynx and other parts of the throat. When radium treatment is available and can be carried out properly, tonsillectomy, as a rule, should not be done.

Physical Therapy in the Treatment of Illnesses Caused by Light, Heat, Cold, Mechanical Irritation, etc.—In the treatment of certain diseases, set rules may be given for the application of physical agents, such as light, heat, cold and mechanical irritation which apply to the average individual and enable one apparently to obtain maximum benefit with a minimum of harmful result. In this paper by DUKE (*Arch. Phys. Ther., X-ray, Radium*, 1928, **9**, 193) are described cases which show that such rules cannot be applied universally. Some individuals are highly sensitive to the action of one or more of the physical agents mentioned. In these the application of physical agents in average dosage causes harmful and even dangerous results. Illnesses in patients of this type caused by physical agents as they are encountered under natural conditions are often extremely severe. The symptoms observed can be classified under such terms as urticaria and dermatitis of greatest severity, rhinitis, cough or asthma, gastrointestinal disturbances of mild or extreme grade, urological disturbances, such as irritable bladder or even renal colic. The fact is, that few tissues are immune to disturbance caused by the effect of physical agents in sensitive individuals. The illnesses are extremely specific and are caused in a given individual usually by one and only one specific physical agent. For example, those caused by light, may be caused by certain rays of light at the violet end of the spectrum and by light only. In those sensitive to cold, symptoms may appear only after exposure to cold between certain specific grades, such as between 5° and 15° C. Brilliant therapeutic results can be obtained through the avoidance of the agent to which the patient is sensitive or through the appropriate application of the

agent in repeated gradually increasing dosage. This frequently gives rise to tolerance. For example, through the use of increasing dosage of light in light sensitive cases, cold in cold sensitive cases, heat in heat sensitive cases or of friction in friction sensitive cases a degree of tolerance can frequently be obtained which enables the patient to withstand such dosage as he encounters under natural conditions—in fact, the agent previously harmful after treatment usually becomes beneficial.

The Roentgenogram in Mastoid Disease.—While emphasizing the substantial aid of roentgenography in mastoid diagnosis, TAYLOR (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 522) insists that it should not outweigh the clinical findings and the latter should furnish the chief guide to procedure. A history of a previous acute otitic infection must be taken into consideration in estimating the significance of a localized area of destruction shown by the roentgenogram. A mastoiditis which shows only mild involvement, as evidenced by decreased illumination and slight destructive changes may clear up without operation. Progress of destructive changes in an acute otic infection indicates that the lesion is active.

Insufflation of Carbon Dioxid in the Roentgen Diagnosis of Tubal Obstruction.—From experience with 66 patients, RUBIN (*Radiology*, 1928, **11**, 115) strongly prefers insufflation with carbon dioxid to the injection of iodized oil for determining the patency of the Fallopian tubes. The gas demonstrates tubal patency or nonpatency, and is rapidly resorbed without trace. It is practically innocuous, is simpler to carry out than the injection of lipiodol, although having diagnostic value equal to the latter, and is superior to lipiodol for demonstrating tubal spasm.

Roentgen Ray Diagnosis of Pulmonary Infection with the Friedländer Bacillus.—KORNBLUM (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 513) holds that Friedländer's pneumonia, which is probably more common than is generally supposed, presents a characteristic roentgenographic appearance, with four definite stages. In the initial stage it greatly resembles ordinary bronchopneumonia, but differs from the latter in that it seldom has a typical, bilateral, basal distribution, and the involvement is most marked peripherally. In the second stage, the bronchopneumonic areas coalesce and imitate lobar pneumonia, except that the consolidations do not follow the anatomic markings of the lobes, and resolution begins at the hilum. In the third stage, which is most characteristic roentgenologically, abscesses, many of which have a demonstrable fluid level, develop in the consolidated areas. Following survival of the third stage the process gradually assumes a chronic nature. An irregular fibrosis occurs with cavities remaining at the site of the previous abscesses. The cavities are thin walled and sometimes difficult to detect. During this period reinfections may occur, the same or new areas passing through virtually the same stages *de novo*.

Roentgen and Radium Treatment of Toxic Goiter.—For toxic goiter STEVENS (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 539) considers that radiation with Roentgen rays or radium is second to no other method of treatment and may be expected to cure about 90 per cent of the patients.

NEUROLOGY AND PSYCHIATRY

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Intractable Chronic Pain in the Lower Segments of the Body. Relief by Means of Sacral Epidural Injections.—VINER (*Arch. Neurol. and Psychiat.*, 1928, **20**, 336) outlines the technique of epidural injection and reports on its use for the relief of pain in sciatica, lumbosacral pain, rheumatoid arthritis, locomotor ataxia, cancer of the rectum, encephalitis, coccygodynia, amputation stump neurologia, traumatic neuritis, endarteritis obliterans, diabetic ulcer of the leg and tumor of the spinal cord. (The author questions this diagnosis.) He concludes that the treatment is effective in the worst and most persistent cases of sciatica, is of decided value in tabetic lightning pains and in many of the other conditions mentioned. "In general, it seems correct to say that this method is efficient in all kinds of chronic peripheral pain originating at or below the third lumbar segment which is not of vascular or sympathetic origin." He warns that in those cases where the injection proves satisfactory the patient should not be discharged as the causal condition may appear later and may require appropriate treatment.

Central Neuritis, its Etiology and Symptomatology.—PEARSON (*Arch. Neurol. and Psychiat.*, 1928, **20**, 366) reports 31 cases found with clinical diagnoses as follows: Involutional melancholia, 2 cases; manic depressive psychosis, depressed type, 2; manic depressive psychosis, mixed type, 2; undiagnosed, but probably toxic exhaustive psychosis, 1; psychosis with somatic disease, 5; senile dementia, 1; schizophrenia, paranoid type, 1; chronic alcoholism, 4; delirium tremens, 2; pellagra, 9; probable pellagra, but diagnosed general paralysis, 1; epilepsy, 1. As to symptomatology and course of the disease, he found that these cases did not differ materially from unselected cases of the analogous symptom complex without central neuritis except in the cases of pellagra in which disease every case showed the pathologic changes. He discusses the possible causes and concludes that it is not caused by axonal injury, infection, starvation, exogenous or known endogenous toxins, nor is it a prelethal condition. "It seems to be the result of some subtle disturbance of metabolism that produces starvation and autometabolism of the cell." He states that the names applied to this condition are misnomers and advances "primary cytolytic degeneration" as a preferable term.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Splenic Mycosis.—Splenic mycosis presents a gross picture characterized by the appearance of yellowish-brown firm nodules found in the trabeculæ of the spleen. They vary in shape and may be scarcely visible or measure several millimeters in diameter. By fusion large infarct areas may be formed. The color of these nodules is chiefly due to the iron pigment, the pigment may become embedded in sclerosed tissue, some nodules may become calcified, the whole area is surrounded by recent hemorrhage. By investigation, JAFFE and HILL (*Arch. Path.*, 1928, **6**, 196) have shown the siderotic nodules of the spleen to contain mycelium and fructification bodies of an aspergillus. This finding has also been found in juvenile splenomegalic anemia, sickle-celled anemia and in tuberculosis of the spleen. It would appear that different types of aspergillus would produce similar changes. The occurrence of the fungus under different types of pathologic conditions does not favor the theory of a disease entity caused by a fungus. Patients have been encountered with splenic anemia whose spleens have shown fungi. Others with the same disease show no fungi. On the other hand, fungus has been found in cases which have splenomegaly without anemia, hence the fungus is not responsible for the anemia. The reactions of the body against the fungus are foreign-body giant cells along with a proliferation of connective tissue. The mycelium absorb iron and calcium salts and are finally buried in sclerosed tissue which may then become calcified. In view of the fact that the aspergillus has been found in both large and small spleens the term "splenic mycosis" is preferred to that of mycotic splenomegaly.

Immunization of Children against Tuberculosis.—This problem has been before the medical world since the tubercle bacillus was discovered. The work of Calmette and his coworkers with an avirulent living culture of tubercle bacilli called B.C.G. (Bacillus Calmette-Guerin) has aroused a tremendous interest in the subject and about 100,000 infants have been treated as a result. PETROFF and BRANCH (*Am. J. Pub. Health*, 1928, **18**, 843) have given an analysis and critical review of the already extensive literature on this topic. They point out that the favorable results reported have been gained largely from impressions and not from facts. It has been shown that from 40 to 90 per cent of children at the age of puberty give a positive Pirquet tuberculin reaction and that the evidence suggests that a high percentage have become infected during the first year of life and in the presence of heavy family dissemination the mortality is high. On the other hand, the ordinary

nonprogressive infection has been considered as responsible for the high degree of resistance in the human race. Because Calmette believes that most infection takes place in the first ten days by the digestive route his vaccinations have all been carried out by feeding the organism to newborn babies. The questions arise: (1) Is it dangerous? (2) Is it effective? The evidence bearing on the pathogenicity of B.C.G. and on the results of vaccination in animals is carefully given and also the preparation of the vaccine and the method applied in infants. The authors' study of cultures of B.C.G. resulted in separing two types of colonies the "R" and "S," the former producing tubercles which heal and the latter progressive disease and death of the guinea pig. They, therefore, suggest that Calmette has by his method of culture permitted the "R" form to predominate without however, completely eliminating the "S" form. The article is full of interesting points on pathogenicity, modes of infection, dissociation, transmutation, filtrable forms and other phases of the problem. The authors consider the other effective sociologic and health measures have decreased the mortality and infection in childhood to a very low level in the United States and Canada and see no reason for introducing this prophylactic measure of vaccination of infants at present. They further say that "The careless use of poor statistics obtained from a study of human beings is going to lead us nowhere" and advocate the study of the problem in cattle on a large scale.

The Gastrointestinal Flora in Pernicious Anemia.—In the past the qualitative study of the intestinal flora has been chiefly applied to the acute infections and has given most satisfactory results in the discovery of such specific organisms as those inducing cholera; dysentery, and so forth. On the other hand, little attention has been paid to the organisms normally present in the intestine. DAVIDSON (*J. Path. and Bact.*, 1928, **31**, 557) presents the possibility that these latter, if increased in numbers and toxicity, may cause some ill-defined medical conditions or have a pertinent bearing on the development of pernicious anemia. This article is the result of a bacteriologic study, quantitative as well as qualitative, made upon the gastrointestinal contents of 41 cases of pernicious anemia. For the sake of comparison, the flora of healthy subjects and of others, showing various pathologic conditions, was investigated. The actual bacteriologic work done was very extensive and in part very ingenious. No claim is made that accurate numerical results were obtained by the quantitative technique; but in spite of many inconstant elements, the author states that, after examining hundreds of specimens from animals and humans, in any given case the bacterial count will remain within a limited range. The differences between normal and pathologic specimens are so great that all minor errors are eliminated. The quantitative studies showed that the feces in pernicious anemia contain more B. coli, more streptococci and especially more B. welchii than are present in normal persons or in others suffering from various diseases. Careful study suggests that the B. welchii are increased 1000 to 10,000 times over the content in healthy cases. The qualitative studies brought forth no evidence which would indicate that any particular variety of the usual strains was associated with pernicious anemia. The organisms studied were B. coli; strepto-

coccus; B. acidophilus; and B. welchii. In pernicious anemia, high bacterial counts were noted in all gastroduodenal contents, but no specific organism was demonstrable, and B. welchii were in relatively small numbers. The author views pernicious anemia as a pathologic rather than an etiologic entity. He looks upon gastrointestinal sepsis as an extrinsic factor which functions by preventing the liver from producing the substance which, as Minot and Murphy have shown, is necessary for the proper maturation of the megaloblasts.

HYGIENE AND PUBLIC HEALTH

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The Action of Currents of Very High Frequency upon Tissue Cells. A. Upon a Transplantable Mouse Sarcoma.—SCHERESCHEWSKY (*Pub. Health Reps.*, 1928, **43**, 927) used a mouse sarcoma strain which gave about 96 per cent of successful takes and which showed but 2 per cent of spontaneous reactions. The apparatus and the technique employed are described. The effect many times is marked and immediate. The result is a coagulation necrosis and rapid solution of the cells seems to occur at times. In one series of mice 96 per cent survived in adequately controlled experiments. **B. Upon A Transplantable Fowl Sarcoma.**—SCHERESCHEWSKY and ANDERVONT (*Pub. Health Reps.*, 1928, **43**, 940) worked with the Rous fowl sarcoma. The results were favorable but less so than with mouse sarcoma. The writers believe the method deserves much more study before its value is determined but consider that it may have important clinical application.

A Unit for Scarlet Fever Streptococcus Antitoxin.—DYER (*Pub. Health Reps.*, 1928, **43**, 1659) reviews previous attempts at standardization of scarlet fever streptococcus antitoxin and proposes as a unit "ten times the smallest amount of scarlet fever streptococcus antitoxin necessary to neutralize one test dose of toxin." Protocols illustrating the use of the unit are given. The unit was designed to be of such value that the dose of the antitoxin used clinically would approximate the clinical dose of diphtheria antitoxin when each was expressed in terms of the respective unit.

The Properties of the Bactericidal Substance in Milk.—JONES (*J. Exper. Med.*, 1928, **47**, 877) studied certain of the properties of the

bacterial agent in milk. He states that the substance is present in the colostrum and milk of the first few days of lactation as well as later. Its concentration varies in the secretion from various quarters of the same cow. Its activity is diminished by heat and cannot be restored again by the addition of active milk. The principle is present in whey and readily passes through the coarsest Berkefeld filter although a considerable portion is retained by N candles. The finest filter (W) completely retains it. It is adsorbed by animal charcoal but not by kaolin, kieselguhr, or bolus alba. It can be desiccated and its presence has been demonstrated in one brand of dried milk.

An Epidemic of Rheumatism at a Cardiac Camp.—Hiller and Graef (*Am. Heart J.*, 1928, **3**, 271) report studies on 10 cases of rheumatism, 1 of chorea and 1 of acute tonsillitis occurring within a short period in a group of children at a cardiac camp. Unusually inclement weather coincided fairly well with the incidence of the cases. Although the weather undoubtedly played a part in their incidence, the authors feel that communicability was also a factor.

The Incidence of Clinical Diphtheria among Family Contacts Subsequent to the Discovery of Carriers.—In 1925 Doull and Lara (*Am. J. Hyg.*, 1925, **5**, 508) published a report on the frequency of clinical diphtheria in families in which carriers of diphtheria bacilli had been previously found. These data included 1044 carriers among white school children in Baltimore. Doull, Stokes and McGinnes (*J. Prev. Med.*, 1928, **2**, 191) studied the incidence of the disease subsequent to the discovery of carriers and reached the following conclusions: (1) That the family contacts of carriers of diphtheria bacilli are exposed, within the *first* month after discovery, to a risk of clinical diphtheria measurably greater than that of a control population living in the same neighborhood, and otherwise considered comparable, but consisting of family contacts of school children cultured and found negative. This is precisely as would be expected from what is known of the epidemiology of the disease. The incidence among family contacts of carriers during this period, is, however, only about one-tenth that of those in similar association with recognized clinical cases. (2) Family contacts of carriers of virulent bacilli seem to suffer a higher risk of attack than do those associated with carriers of bacilli of the so-called "avirulent" type, but there is some doubt whether the proof of this is statistically adequate. Nevertheless, diphtheria incidence in the latter group is, in turn, significantly higher than among the control families. This strongly suggests that those who harbor diphtheria bacilli classified as avirulent according to the usual tests may be of some importance in the spread of the disease. The brief period of increased incidence in the families of carriers is followed by a compensatory period of at least two months' duration in which the attack rate falls below that of the control group. This may be due to a lessened exposure due to a considerable proportion of the carriers gaining immunity to the carrier state, or to immunity acquired by other members of these families through contact with the carrier, or possibly to a combination of both these factors.

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Some Studies of the Pyloric Sphincter.—J. EARL THOMAS (from the Department of Physiology of the Jefferson Medical College). This report comprises a study of the action of epinephrin on the pyloric sphincter *in situ* and of epinephrin, pilocarpin, atropin, and barium chlorid on the excised pyloric sphincter, of dogs, cats and rabbits.

Graphic records of changes in the tonus of the pyloric sphincter in operated animals under ether anesthesia were obtained by means of a manometer measuring the pressure necessary to force a stream of air of constant volume through a flexible tube lying in the pyloric canal. The stream of air was automatically kept constant by means of a mechanism operating on the principle of a pressure-reducing valve.

Studies of the excised pyloric sphincter have not given satisfactory results in the past due to the failure of the sphincter to manifest a reasonable degree of irritability after excision. This difficulty was obviated by the use of a closed bath in which an oxygen pressure of one atmosphere could be maintained and by regulation of the pH of the bath between 7.6 and 7.8. Deterioration of the tissue after excision was avoided by keeping it in an oxygenated solution at about zero degrees centigrade while dissections were being made. Locke's solution without dextrose was used for the bath.

The primary action of epinephrin on the pyloric sphincter *in situ* may be to cause either increase or decrease of tonus, the former when the muscle is relaxed and the latter when it is contracted. However, increase of tonus in the cat and decrease of tonus in the rabbit were produced but rarely. Large doses of epinephrin had a tendency to cause contraction of the spincter in the dog and rabbit. Relaxation occurred in the rabbit only with minimal doses given when the tonus of the sphincter was high. Epinephrin generally inhibited the rhythmic contractions in all of the animals.

Epinephrin caused slight contraction followed by more pronounced relaxation of the excised pyloric sphincter of the dog, slight relaxation in the cat, and pronounced contraction in the rabbit sphincters. The results are in accord with the reactions most commonly seen under average conditions in the sphincters *in situ* of the same species. Changes in the tonus of the muscle did not affect the reactions of the excised sphincters, except in degree.

A secondary increase in tonus and augmentation of rhythmic contractions followed the primary effect of epinephrin in the sphincters *in situ* but not in the excised sphincters. It was therefore regarded as an indirect effect in the operated animals not indicative of a direct stimulating action of epinephrin on the pyloric motor mechanism.

The results with epinephrin are interpreted as indicative of a slight

preponderance of inhibitory over motor components in the thoracolumbar sympathetic innervation governing the tonus of the pyloric sphincter in the dog and cat and marked preponderance of motor over inhibitory components in the rabbit. The sympathetic innervation governing the rhythmic contractions is apparently mainly inhibitory in all three species.

The results with pilocarpin and atropin were for the most part a confirmation of previous observations. Pilocarpin caused a moderate increase of tonus and initiated or augmented rhythmic contractions. Atropin caused cessation of rhythmic contractions and slight loss of tonus and manifested its usual antagonism for pilocarpin. Barium chlorid caused marked increase of tonus and augmentation of rhythmic contractions. No species differences were apparent in the reactions to these drugs.

Morphin was sometimes used to supplement the ether anesthesia in prolonged experiments in operated animals, and whenever administered, it increased the tonus and rhythmic activity of the sphincter to a greater extent than either pilocarpin or epinephrin.

The Glass Electrode.—William C. Stadie and Effie Ross Hawes (from the Department of Research Medicine, University of Pennsylvania). The glass electrode was found to give satisfactory measurements of the pH of phosphate solutions to ± 0.01 pH units. A modification of the electrode vessel was devised which facilitated the measurement of the pH of CO_2 containing solutions without loss of CO_2 and which would therefore be adaptable to serum and blood. The apparatus was further simplified by the addition of a projecting microscope to project the image of the indicating electrometer needle. The amount of necessary shielding was reduced to a convenient amount and a simple electrically controlled switch introduced.

The Excretion of Morphine.—W. A. Wolff, C. Riegel, E. G. Fry (from the Laboratory of Pharmacology of the University of Pennsylvania). The problem of the excretion of morphine in relation to the development of tolerance has been restudied with the aid of a new method for estimating morphin in biologic material, in which certain errors inherent in older methods are avoided (*J. Biol. Chem.*, 1928, **80**, 379). The accuracy of the method when applied to urine is very satisfactory; less so for feces, the results being consistently high. Hence the fecal excretion is, in all probability, represented as too great.

Normal dogs, each given a single dose of morphin the size of which varied between 25 mg. and 200 mg. per kilo body weight, eliminated 11 to 23 per cent in the urine; feces contained from traces up to 7 per cent. The percentage elimination is of the same order regardless of size of dose. Similar differences in urinary elimination are encountered in litter mates or in the same dog when he in injected more than once.

During the development of tolerance by repeated daily injections the percentage of morphin eliminated did not change either consistently or significantly. A series of four dogs tolerant to doses ranging from 25 mg. to 60 mg., which had been kept on a morphin régime for periods varying from seven to five hundred and forty-three days, gave 10 to 14 per cent elimination in urine; 2 to 6 per cent in feces. Hence tolerance

is not characterized by significant increase in capacity to destroy morphin as was held by Faust (*Arch. f. exper. Path. u. Pharm.*, 1900, **44**, 217) and later by Teruuchi and Kai (*J. Pharm. and Exper. Ther.*, 1927, **31**, 177).

A few data on excretion by the human addict roughly parallel those for tolerant dogs.

Gastric Motility in Vitamin-B Deficiency.—W. B. Rose, C. J. Stucky and G. R. Cowgill. In 1917 Osborne and Mendel observed that anorexia was a prominent symptom of vitamin-B deficiency in rats. Likewise in 1920 Karr noted that dogs lose their appetite when deprived of vitamin-B. Cowgill and others (1926) investigated the motor function of the stomach in vitamin-B deficient dogs and reported that in the advanced stages of this deficiency, when anorexia was associated with nervous and muscular symptoms there was gastric atony.

However, this assertion of the occurrence of gastric atony in the presence of neuromuscular symptoms of vitamin-B deficiency, brought forth the criticism by an eminent investigator that the gastric atony observed, was in all probability due to the fact that the animal was moribund. This interpretation was strengthened by the work of Erma Smith (1927) who reported that tracings of gastric motility of vitamin-B deficient dogs were indistinguishable from those obtained in normal controls.

In view of this conflicting evidence, a study of the hunger contractions in B-avitaminotic dogs was undertaken with certain definite modifications in procedure. Thus a series of control animals were employed, each of which received the same amount of food and water daily that was consumed by a corresponding deficient dog. In addition the controls were given their full quota of vitamin B daily regardless of their food and water intake. In this way an attempt was made to duplicate, insofar as possible, nutritive changes resulting from vitamin-B deficiency, leaving a lack of vitamin B as the only known variable. Parallel blood studies were made on both control and deficient animals throughout the experiment. A technique was developed which made it convenient to record hunger contractions, continuously over a period of twenty-four hours or longer.

In general the results point to the fact that there is a distinct decrease in the motor power of the stomach in vitamin-B deficiency. In two animals gastric atony was recorded for periods of over fifty and one hundred hours respectively. This atony occurred a week or more *before* neuromuscular symptoms developed. Liberal administration of material rich in vitamin B resulted in a return of the normal gastric tonus, rhythm and hunger contractions.

Although none of the control animals developed gastric atony, they manifested a definite decrease in gastric motility. However, one control dog continued to show normal vigorous hunger contractions throughout. This is of particular interest and will be referred to again.

The decrease in gastric motility observed in the present study cannot be attributed to hyperglycemia, because the blood-sugar level remained well within the normal range in all cases throughout these experiments.

On the other hand our data seem to indicate that vitamin-B deficiency

is associated with a variable increase in blood concentration. It seemed that the depression in gastric motility was related to some extent at least to changes in blood concentration. The same appeared to hold true for the food- and water-control dogs. The control animal which did not manifest any decrease in gastric motility was the only one in which the blood concentration did not vary throughout.

Normal dogs, fed a diet complete in every known respect, including an adequate supply of vitamin B, were deprived of water. When the hemoglobin had increased approximately 20 per cent, gastric atony prevailed in all cases. Administration of fluids was soon followed by a decrease in blood concentration and a return of the normal hunger contractions.

In conclusion it may be stated that vitamin-B deficiency is associated with a definite decrease in gastric motility, and that one contributing factor has been demonstrated.

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